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CONTENTS

BENBOW, EDWARD P., JR., SMITH, DAVID T., AND GRIMSON, KEITH S. Sulfonamide Therapy in Actinomycosis. Two cases Caused by Aerobic Partially Acid-fast Actinomyces.. 395

YOSKALKA, J. S. Atypical Pneumonia Simulating Pulmonary Tuberculosis..... 408

HILL, HIBBERT WINSLOW. "Speed of Reaction" Hypothesis. Its Numerical Foundations in Respect to the Tubercle Bacillus..... 414

HOWE, JOHN S., AND MAYNE, ALVIN. Influence of Environmental Factors on Fever in Pulmonary Tuberculosis..... 423

GORDON, BURGESS L., CHARR, ROBERT, AND SOKOLOFF, MARTIN J. Basal Pulmonary Tuberculosis. Results of Treatment..... 432

REISNER, DAVID. Boeck's Sarcoid and Systemic Sarcoidosis. (Besnier-Boeck-Schaumann Disease.) A Study of Thirty-five Cases..... 437

COHN, MAURICE L. Growth of Human Tubercle Bacilli under Restricted Air Conditions 463

Books..... 471

American Trudeau Society..... 480

Abstracts..... 33

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SULFONAMIDE THERAPY IN ACTINOMYCOSIS[1,2]

Two Cases Caused by Aerobic Partially Acid-fast Actinomyces

EDWARD P. BENBOW, JR., DAVID T. SMITH AND KEITH S. GRIMSON

Recent reports (2, 5, 6, 9, 10, 14, 19, 20, 21, 22, 23, 25, 28) suggest that actinomycosis of the Wolff-Israel type responds to therapy with the sulfonamides. The causative agent in this type of actinomycosis is anaerobic and usually produces the so-called "sulfur granules" in the tissues.

We have been unable to find a report of sulfonamide therapy in patients infected with aerobic actinomyces.

In 1881, Eppinger (12) isolated an aerobic, acid-fast actinomyces from a fatal case of brain abscess in man and described it under the name of *Cladothrix asteroides*. The name was changed to *Actinomyces asteroides*, and is now called *Nocardia asteroides*. In 1921, Henrici and Gardner (16) were able to find 26 cases which had been reported prior to that time, all of which were caused by aerobic acid-fast actinomyces. These causative organisms fell into 3 different types or strains: first, Eppinger's strain, or *Nocardia asteroides*, which is characterized by a growth of mealy consistency on solid medium, varying from pale yellow to deep orange in color. It does not liquefy gelatin or peptonize milk and is more pathogenic for guinea pigs than rabbits. The second, a strain isolated by Aoyama (1), differed from *Nocardia asteroides* only in the whitish color of the growth and the darkening of the medium. The third strain was one isolated and described by Birt and Leishman (4) which is characterized by a snow-white growth on solid medium. It does not liquefy gelatin but does peptonize milk and is pathogenic for guinea pigs.

All of these 26 cases but 3, one of which was a case of Madura foot cured by amputation and 2 cases of postoperative peritonitis, were apparently pulmonary in origin; and all 26 cases except the one of Madura foot were fatal.

After reviewing these previously reported cases, Henrici and Gardner reported in full the case of a thirty-one year old, white female with a chronic pulmonary disease. From this patient's sputum they were able to isolate, culture and study the characters of an acid-fast actinomyces which differed from the 3 types or strains previously described. It was characterized by "its proteolytic activity, as evidenced by the alkaline coagulation of milk (rennin), the digestion of coagulated casein, the rapid liquefaction of gelatin and the darkening of medium containing peptone (tyrosinase)." Because of the chalky-white appearance of the growth on media, this fourth strain was called *Nocardia gypsoides*.

At a later date Henrici[3] expressed the belief that the species *N. asteroides* varied through a wide range, and that if we continued to multiply species on the

[1] From the Departments of Medicine, Bacteriology and Surgery, Duke University School of Medicine, Durham, North Carolina.

[2] A part of the cost of this study was borne by a grant from the John and Mary R. Markle Foundation.

[3] Personal communication to Dr. Norman F. Conant in 1939.

basis of small differences in biological characters, we would have about as many species as cases. He was inclined to agree with Baldacci (3) who proposed reducing *N. gypsoides* and relative strains of the aerobic acid-fast actinomyces with only minor differences in their biological characters all to the rank of variants of *N. asteroides*.

Goldsworthy (13), in 1937, reported a case of pulmonary actinomycosis in an Australian male of sixty-nine years which terminated fatally. The organism which he isolated occurred in the sputum in slender, branching filaments without tangled masses or "granules." No clubs were seen. The organism produced a snow-white colony on solid media, produced a strongly alkaline reaction with litmus milk and did not liquefy gelatin. It must be classified then as a variant of *N. asteroides*.

In 1938, Kessel and Goolden (18) reported a comparison of strains of actinomyces recovered from human lesions. Included was one case of fatal termination where cultures taken from the lungs and meninges yielded an acid-fast aerobic actinomyces which did not produce granules but was dispersed in branching filaments and which seemed identical with *N. asteroides* 323 from the American Type Culture Collection.

CASE REPORTS

Two patients infected with aerobic actinomyces have been successfully treated by employing sulfonamides in addition to conventional therapeutic measures, and these cases will be reported.

The patient described as case 1 developed weakness and loss of weight, and the X-ray film showed an infection of the left lung. While she was being treated with rest in bed, three draining sinuses appeared in the neck, chest and hip. She was transferred from a sanatorium to our hospital for investigation of a possible mycotic infection. Acid-fast actinomyces were found in the sputum and in the drainage from the sinuses. After seven months' treatment with bed-rest, vitamins, sulfonamides, X-ray therapy, surgical drainage and potassium iodide, the patient made slow but steady improvement; and she is now apparently well.

Case 1: M. C., history number A-72036, white farmwife of thirty-six, was admitted to Duke Hospital on October 13, 1941, complaining of draining sinuses on the right side of the neck and on the right shoulder and the left hip of four months' duration. The past history was negative.

The present illness began in April, 1941, with weakness, malaise and weight loss. She was seen by her local physician who reported that X-ray films of the chest showed clouding of the left lung. She was put at bed-rest. Her general condition improved very little, and one month after the onset of her illness she developed a swollen, tender "pimple" on the right side of her neck just below the ear. This was incised by her physician and, instead of healing, continued to drain purulent material. Shortly afterwards she developed similar lesions on the left hip, on the back and in the right infrascapular region. These were incised and also continued to drain purulent material. She was given oral sulfanilamide of unknown dosage for two weeks after the incision of these areas, but this was discontinued because of persistent nausea, vomiting and loss of appetite. During the next two months she developed a cough, productive of moderate amounts of purulent

sputum, night sweats and fever of a moderate degree each afternoon. She lost 50 pounds during the course of this illness.

She was then studied in a nearby sanatorium, and was referred to Duke Hospital with a preliminary diagnosis of "a fungus infection."

Physical examination: Temperature 37.8°C. (100.2°F.), pulse 108, respirations 20. She appeared chronically ill and greatly emaciated. She presented three obvious lesions, one at the angle of the right jaw surrounded by a raised area of granulation tissue, another about 2 cm. in length in the right infrascapular region with clean-cut granulating edges and profuse drainage of thick yellow pus but with little surrounding induration and a third just above the left iliac crest, 5 cm. in length, with some surrounding scar formation and also draining pus freely. The percussion note was impaired over the left upper chest and breath sounds were diminished in this area. The abdomen was slightly tender, the liver edge palpable 4 cm. below the right costal margin, smooth and somewhat tender. X-ray films of the chest showed infiltration and pleural reaction through the entire left lung and old calcium deposits in the right hilar region (figure 1).

Laboratory examination revealed red cells 3,900,000, haemoglobin 10.2 g. (66 per cent), white cells 28,120; differential: polymorphonuclears 81 per cent, large lymphocytes 2 per cent, small lymphocytes 10 per cent, monocytes 7 per cent. The Wassermann test was negative. Urine examination was also negative. Tuberculin test (OT 1:10,000) was negative. Sputum examination was negative for tubercle bacilli, but revealed many gram positive branching mycelia which stained acid-fast. Sputum culture on beef-infusion-blood agar and incubated at 37°C. for one week showed growth of aerobic white actinomyces which stained acid-fast. Sputum culture on Sabouraud's medium at room temperature for three weeks showed growth of aerobic white actinomyces which also stained acid-fast. Smears taken from the open lesion on the patient's back showed branching mycelia which were acid-fast and, also, actinomycotic granules without club formation. This fresh material, injected intraperitoneally in guinea pigs, killed them in three weeks; innumerable tiny, tubercle-like lesions were found studding all exposed peritoneal surfaces. Acid-fast branching mycelia were demonstrated in these tubercle-like lesions, and from them white aerobic actinomyces were cultured on beef-infusion-blood agar when incubated at 37°C. for one week. Because of the mycelial growth, animal pathogenicity and cultural and staining characteristics, it was thought that this organism was identical with the strain Henrici named *A. gypsoides* and later renamed *Nocardia asteroides*.[4]

The patient gave a negative skin test reaction to intracutaneous injection of 0.1 cc. heat-killed vaccine prepared from the organism cultured from the lesions. Dr. Donald S. Martin performed complement fixation tests of the patient's own serum against the organism and obtained negative results.

The patient remained in the hospital seven and one-half months. Treatment consisted of a three weeks' trial on sulfanilamide, followed by X-ray therapy, local compresses, potassium iodide in large doses, multiple surgical drainages and excisions of the sinuses, multiple blood transfusions and general supportive measures. She ran an irregular, spiking fever and failed to gain weight during the first eighteen weeks of hospitalization. During the last fifteen weeks, however, she improved markedly, gained from 33 to 47 kilos in weight and showed progressive healing of the sinus tracts. Her course was complicated by a period of confusion and disorientation, during which she had to be tube-fed; the development of multiple subcutaneous abscesses, none of which were found to contain

[4] This culture was identified by Dr. Norman F. Conant, mycologist for the Duke Hospital.

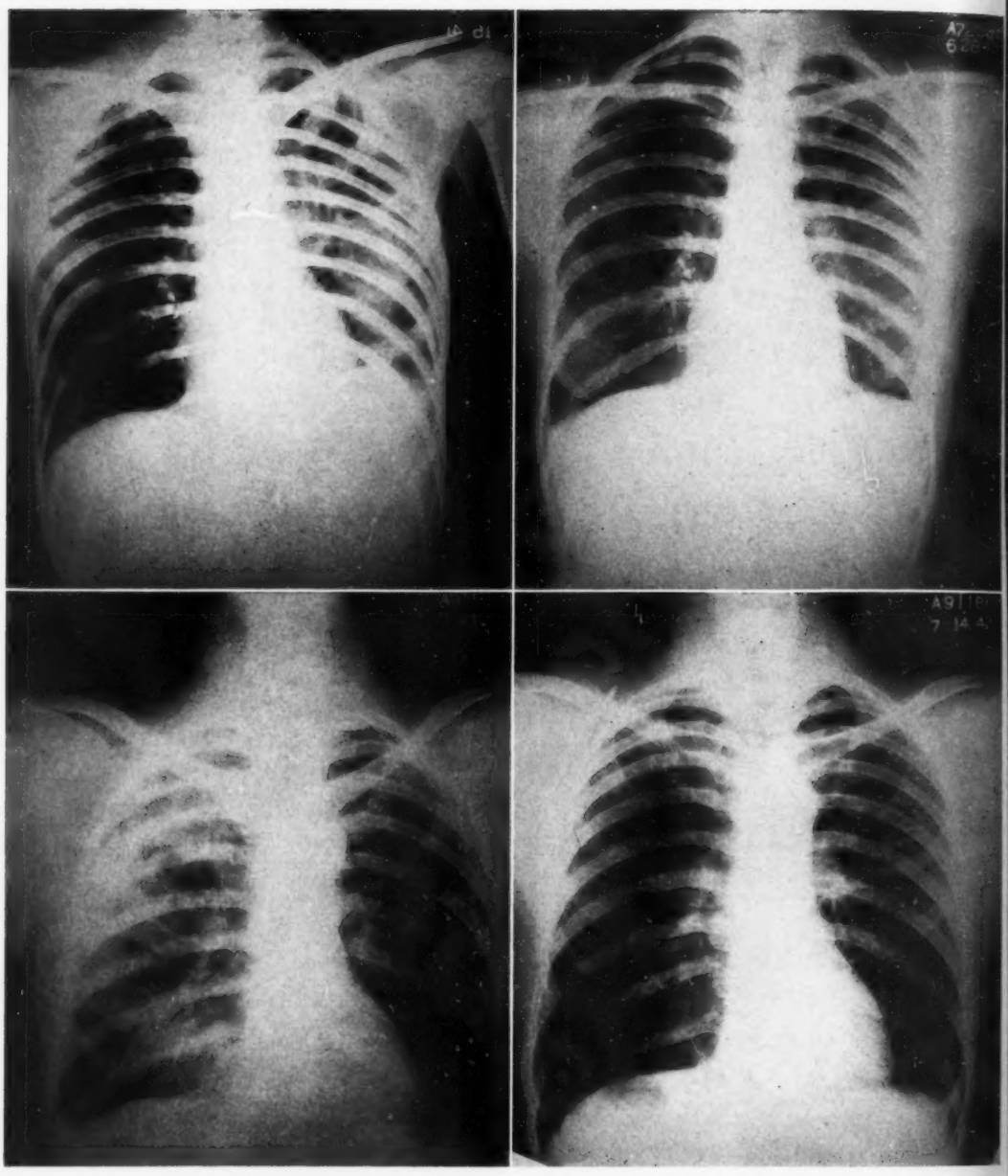

FIG. 1 (Upper left). Case 1. Chest roentgenogram May 15, 1941. Shows elevation of the diaphragm on the left, with some narrowing of the interspaces. There is a dense lesion in the central portion of the lower two-thirds of the left lung. Some areas of calcification are seen in the right hilar region.

FIG. 2 (Upper right). Case 1. Chest roentgenogram June 28, 1943. The calcified areas in the right lung are unchanged. The massive lesion in the left lung has disappeared, leaving some thickening of the pleura and adhesions to the diaphragm.

FIG. 3 (Lower left). Case 2. Chest roentgenogram November 21, 1942. Shows extensive infection in the upper two-thirds of the right lung and another dense area above the diaphragm. The areas of rarefaction in the right upper lobe are probably cavities since the patient was producing several ounces of bloody sputum when this film was made.

FIG. 4. (Lower right) Case 2. Chest roentgenogram July 14, 1943. Shows complete resolution of the infection in the right lung except for slight residual fibrosis in the right apex.

actinomyces; the development of paronychiae, requiring the removal of both large toe nails; and herpes zoster around a right lumbar segment.

She was discharged on May 31, 1942 on potassium iodide, and was seen again in July, 1942, and June, 1943, with all sinuses healed and without complaints. Follow-up X-ray examination of the chest in June, 1943 was essentially clear, except for the old calcium deposits in the right hilar region (figure 2).

The patient described as case 2 developed an abscess in the subcutaneous tissues of the chest wall, followed by the appearance of multiple abscesses of the lung and a perirectal abscess. Acid-fast actinomyces were found in the sputum and in the perirectal abscess.

With surgical drainage of the chest wall abscess, surgical and X-ray therapy for the perirectal abscess, supplemented by sulfadiazine and potassium iodide, the patient improved steadily.

Case 2: F. S., history number A-91186, a white farmer of fifty-two years, was admitted to the surgical service of Duke Hospital on September 8, 1942, complaining of a tender swelling over the left chest of one week's duration. Past history was negative, as was the family history.

The patient was in good health until the beginning of August, 1942, when he developed a cough and slight fever. His illness was diagnosed "influenza." This febrile illness lasted one week, but the patient was left with a slight cough productive of small amounts of phlegm which persisted until admission. He continued to grow weaker and lost 20 pounds in weight. About two weeks before admission he noted aching through the left upper arm which was aggravated by motion, and one week before admission he developed a swollen, slightly tender area over the left lateral posterior chest wall which continued to swell. He had some fever and a few "night sweats" during the week before admission; and because of these symptoms, he was referred to Duke Hospital by his local physician.

Physical examination: Temperature 37.8°C. (100.1°F.), pulse 102, respirations 22, blood pressure 130/72. The patient showed evidence of recent weight loss and appeared chronically ill. The skin was pale, loose and dry. The teeth were carious. The left axillary lymph nodes were discrete, slightly enlarged and somewhat tender. The left upper arm and shoulder joints were tender to motion and palpation, and motion of the left upper arm was limited to 90 degrees abduction because of pain in that area. There was a tender, fluctuant swelling, measuring 6 to 7 cm. in diameter, in the lateral portion of the left chest wall posteriorly and overlying the lower portion of the left scapula. Examination of the lungs was negative. There was a moderately loud systolic murmur over the precordium which was transmitted into the neck vessels. The liver edge descended 1 to 2 cm. below the right costal margin on inspiration, but was not tender and felt smooth. X-ray films of the chest showed the lung fields clear. The left costophrenic angle was somewhat obscured, possibly by adhesions. The heart and ribs appeared normal. A soft tissue mass was also noted in the region of the left axilla.

Laboratory studies showed red cells 3,250,000, haemoglobin 12 g. (78 per cent), white cells 18,200; differential: polymorphonuclears 89 per cent, small lymphocytes 10 per cent and monocytes 1 per cent. The Wassermann test was negative. Urine examination showed a trace of albumin, 3 to 5 white cells per high power field and an occasional granular cast.

The fluctuant mass on the left posterior chest was incised and drained on the second hospital day, with the removal of 30 to 40 cc. of gray-green pus. A rubber drain was placed in the abscess cavity. The wound was packed open with vaselin gauze. Cul-

tures of the abscess pus revealed an occasional colony of *Staphylococcus aureus* which may have been a contaminant. The patient was discharged on the sixth hospital day in care of his local physician.

When next seen on October 13, 1942, one month after discharge, the patient stated that the incision had continued to drain purulent material, that he had continued to have low-grade fever at night and that one week previously he had developed pain in the right shoulder and upper arm.

Physical examination: Temperature 36.6°C. (98°F.), pulse 104, respirations 26, blood pressure 122/72. He appeared chronically ill. The skin was loose and dry. There were no palpable lymph nodes. There was a 4 cm. sinus over the left sixth rib, laterally and posteriorly, which drained purulent material. Examination of the lungs revealed the percussion note to be resonant, breath sounds vesicular but slightly diminished over the right medial chest posteriorly. There were no râles. The systolic murmur was again present as previously described. Just anterior to the anus there was a fluctuant, very tender swelling, 2 cm. in diameter. Rectal examination was otherwise negative.

Laboratory examination revealed haemoglobin 9.9 g (64 per cent), white cells 8,050. Urine examination was negative. The Wassermann test was negative. X-ray films of the chest showed an area of infiltration in the right upper lobe. Reëxamination the following day showed a decided increase in the process. Several small areas of rarefaction were present in the infiltrated area. These may have represented cavitation. Films of the shoulders were normal. Sputum examinations showed some blood, but were repeatedly negative for tubercle bacilli. The perineal abscess was incised and drained. Cultures from this abscess showed *Staphylococcus aureus*. Biopsy taken from the margin of the thoracic sinus showed acutely inflamed granulation tissue. No specific organisms were seen. The patient ran a somewhat febrile course and was given sulfathiazol orally and, later, sulfadiazine by mouth sufficient to maintain the blood level at 10 to 15 mg. per 100 cc. At one time during his febrile course the patient became mentally confused, had a generalized tonic convulsion and fell from his bed, striking the right zygoma. Crepitus was later felt in this region. There was noted at this time a left lower facial weakness, a bilaterally positive Babinski reflex, sustained ankle clonus on the right and unsustained ankle clonus on the left. Knee and ankle reflexes were hyperactive but equal. Lumbar puncture showed the spinal fluid to be clear, under no increased pressure and containing no cells. Culture of this fluid was negative. It was the consulting neurosurgeon's impression that the patient had a "metastatic" brain abscess, the exact site being undetermined. The patient's mental confusion quickly cleared. He was skin-tested to *Blastomyces* and *Monilia* antigens, both tests being read as negative. He was discharged on the fourteenth hospital day, after having been afebrile for one week.

He improved at home for one month and was without fever. His neurological signs and symptoms disappeared until November 18, 1942 when he had another generalized convulsion and was readmitted to the hospital on November 20, 1942.

Physical examination: Temperature 36.7°C. (98°F.), pulse 72, respirations 24, blood pressure normal. The patient appeared chronically ill, as on previous admissions. There was a defect of the right zygoma, but no tenderness. Neurological examination was negative. Examination of the chest showed dulness and râles over the entire right chest with scattered râles over the left chest. There was a systolic murmur over the pulmonic area which was transmitted to the neck vessels. The red cells were 4,000,000, white cells 10,600; differential: polymorphonuclears 84 per cent, eosinophils 1 per cent, small lymphocytes 11 per cent and monocytes 4 per cent. Kahn and Kline tests were negative. Blood culture showed no growth in five days. Urine was normal. X-ray examination of

the chest showed some increase in the process in the right upper lobe and definite spread to the right lower lobe so that there was a large area of increased density to the right of the heart. The left lung was clear (figure 3).

The patient was bronchoscoped on the fourth hospital day. A small amount of purulent secretion was present. All lobe orifices were free. There was no evidence of neoplasm or fungus disease. Specimens of bronchial secretions were taken for guinea pig inoculation, fungus culture and staining. The guinea pig inoculated with secretions after treatment with sodium hydroxide gave at a later date a negative skin test reaction to tuberculin and showed no evidence of disease when autopsied after sixty days. The sputum removed at bronchoscopy showed branching forms of mycelia which were identified as actinomyces. These stained both gram positive and acid-fast. Culture of the material taken at the time of bronchoscopy showed a growth of *Nocardia asteroides*. The patient was given transfusions and accessory vitamins in large quantities. He began to improve, gained weight and was discharged on the thirty-first hospital day. X-ray examination of the chest before discharge showed possibly some clearing of the right lung as compared with films taken two weeks earlier, but there was still a diffuse mottling throughout the right upper lobe.

The patient returned to the hospital much improved on March 2, 1943, complaining of continued drainage from the perineal sinus. Examination revealed a sinus tract communicating from the rectum to the perineum. The red cells were 4,600,000, haemoglobin 92 per cent, white cells 5,000; differential normal; serology negative; urine normal. X-ray film of the chest showed a residual fibrosis of the right upper lobe. Culture from the perineal fistula was positive for branching forms of acid-fast actinomyces. The sinus tract was opened freely into the rectum at operation. A pocket containing granulation tissue was found 2 cm. deep along the sinus tract which extended toward the coccyx. This was opened into the rectum, curetted thoroughly and packed. The patient was given sulfadiazine and potassium iodide orally, and the anal and perineal regions were treated with X-ray. He responded well and was discharged on the sixteenth hospital day. In March, 1943, a culture taken from the anal lesion was negative for actinomyces and by November 8, 1943 it had healed. He felt fine, had no complaints, and was advised to continue taking potassium iodide as prescribed and to return for check-up at two to three month intervals. X-rays film, July 14, 1943 showed the lungs clear, except for a slight residual fibrosis of the right apex (figure 4).

DISCUSSION

The name *Actinomyces* (ray-fungus) was introduced by the botanist Harz to describe the fungus granules which Bollinger discovered in 1877 in a cow which was suffering with the disease known to veterinarians as "lumpy jaw." The extensive investigations of J. Israel and M. G. Wolff established the frequency of the disease in man and the identity of the infecting organism with that found by Bollinger in the cow. *Actinomyces bovis* is essentially anaerobic, although some strains will grow aerobically after a number of transfers. The actinomycotic granule, with its clubbed ends, which is so characteristic of the infection in the tissues, does not appear in cultures. Smears of the isolated colonies show branching filamentous organisms which stain blue with the Gram stain.

Bostroem, in 1890, described cultures isolated from clinical cases of actinomycosis which contained organisms morphologically identified with the cultures of Israel and Wolff, but his cultures grew aerobically at room temperature. It is

known now that many of Bostroem's cultures must have been saprophytic actinomyces from the soil, but some aerobic organisms of this type are pathogenic for animals and man. Cope (7) states in his monograph on actinomycosis that infections with the aerobic type are frequently more rapidly fatal than those caused by *Actinomyces bovis*. The anaerobic type of organism is found in approximately 90 per cent of the cases of clinical actinomycosis and the aerobic type in the remaining 10 per cent.

The aerobic actinomyces divide into two groups. The larger number (24) show no tendency to retain the stain when stained by the usual method for demonstrating acid-fast organisms. The smaller group is composed of organisms which are partially acid-fast, but they are never as resistant to decolonization as the tubercle bacillus.

Both groups of the aerobic type of organism are frequently described in the American and English literature as *Streptothrix* and in the French and South American literature as *Nocardia*. Henrici studied over a period of years organisms of the acid-fast type, and he prefers the term *Nocardia*. Waksman, who is an authority on actinomyces from the soil, has collaborated with Henrici in a recent article (27) on this problem, and they conclude that the name should be *Nocardia*.

The signs, symptoms, course of the disease and response to treatment are so nearly identical in the two types of infection that we are taking the position that the *disease* should be called actinomycosis.

Our 2 cases illustrate some of the problems encountered in differential diagnosis and treatment.

DIFFERENTIAL DIAGNOSIS

Pulmonary actinomycosis must be differentiated from tuberculosis, pulmonary abscess and empyema, neoplastic disease of the lungs, tularaemia and other pulmonary mycoses, especially blastomycosis, coccidioidomycosis, cryptococcosis and sporotrichosis. All these diseases may be complicated by one or more draining sinuses over the thorax. The yeast-like fungi—*Blastomyces dermatitidis*, *Coccidioides immitis*, *Cryptococcus hominis* and *Sporothrichum*—grow readily on tubes of Sabouraud's media at room or incubator temperature. The colonies may be slow in making their appearance, and the cultures should be kept for three or four weeks before being discarded as negative. Tularaemia can be eliminated by the specific agglutination test. Chronic tularaemia practically always gives a positive agglutination test in a dilution of serum of 1:1,000, or even higher. Neoplasms of the lung may become secondarily infected with saprophytic acid-fast organisms which are so common in the soil. Guinea pig inoculations will be negative for turerculosis. These saprophytic acid-fast organisms will not grow on ordinary laboratory media; or if cultures are obtained, their lack of pathogenicity can be demonstrated by inoculation into guinea pigs. The conclusive diagnosis of neoplasm will have to be established by biopsy through the bronchoscope, by operation or by necropsy.

The diagnosis of pulmonary abscess, with or without draining sinuses, depends

upon the elimination of the other possibilities and the demonstration of organisms capable of producing pulmonary abscesses.

Tuberculosis presents the most difficult problem in these cases where there are acid-fast organisms in the sputum or in the secretions of the sinuses. Isolated fragments of the mycelium are readily mistaken for tubercle bacilli (figure 5), but a careful study of the whole slide should reveal a number of organisms which are larger than typical tubercle bacilli and show one or more branches. While branching has been described for tubercle bacilli, it is rarely seen. In contrast to tubercle bacilli, treatment with sodium hydroxide kills the acid-fast actinomyces. In both of the cases presented here the guinea pigs failed to develop lesions following the injection of sputum which had been concentrated by the sodium hydroxide

FIG. 5. Kodachrome film of acid-fast organisms found in the sputum of case 2. Other areas in the same slide showed much longer and more branched acid-fast organisms.

method, although the acid-fast organisms were known to be present in abundance in the original material. When fresh sputum from case 1 was injected into guinea pigs, a definite infection was produced, and the branching acid-fast organisms were found in the lesions. Pure cultures of the acid-fast actinomyces will infect guinea pigs and rabbits. If large doses are used, the animals die within a period of four to ten days. With small doses, a transitory infection is induced which goes on to complete healing. Our limited experiments confirm the results of the comprehensive study recently published by Drake and Henrici (11).

It should be noted that the patient reported as case 1 had no complement-fixing antibodies in her serum for her own organism and that an intracutaneous skin test performed with 0.1 cc. of a heavy suspension of a heat-killed vaccine

failed to elicit a positive reaction. At the time these studies were done the patient was in a very debilitated state and may have been anergic. Unfortunately, the tests could not be repeated after her recovery because the cultures were lost. Some years ago Henrici reported that vaccines from actinomyces gave positive skin tests in normal persons and negative skin tests in infected patients. This anomalous finding can now be explained by the new work of Drake and Henrici (11), who report that the cells of the organisms are toxic to normal animals, if we assume that the negative reaction in the infected patient is the result of the anergic state. Cross agglutination and cross complement fixation have been demonstrated by Henrici and Nelson (17) and others between tubercle bacilli and these acid-fast actinomyces. The recent excellent study by Drake and Henrici (11) shows that the allergy induced in guinea pigs by the acid-fast actinomyces (*Nocardia*) is specific and there is no cross reaction with tuberculin. The tests were performed with both a protein and a carbohydrate fraction of the acid-fast actinomyces. A skin test, with the protein fraction, might prove useful in differentiating this type of actinomyces from tuberculosis.

During the past fifteen years one of us (D. T. S.) has encountered 5 cases of pulmonary infection where acid-fast organisms were found in abundance in sputum concentrated by the sodium hydroxide method; and yet, guinea pigs were not infected by the injection of the material. Some of these acid-fast organisms showed branching and some did not. We were not able to cultivate these organisms. Some of the attempts were made from the concentrated material which, we know now, kills the organism. Other failures were probably due to poor technique, but the possibility still remains that acid-fast organisms may be found in the sputum which cannot be cultivated. Nevertheless, tuberculosis can be ruled out by guinea pig inoculation with the concentrated material known to contain the acid-fast organisms.

We do not know whether methods of concentration other than with sodium hydroxide also kill the acid-fast actinomyces. If the organisms are not killed, then cultures made for tubercle bacilli may show a growth of a chromogenic, acid-fast organism which will produce a local lesion in the groin of a guinea pig and yet not be a tubercle bacillus. This possibility of error can be eliminated by subjecting the culture to the sodium hydroxide treatment and then inoculating guinea pigs.

It is quite likely that a number of cases of actinomycosis caused by the acid-fast type of organism have been incorrectly diagnosed tuberculosis. Before there was any hope of a specific treatment, this error was not serious; but now that we have a treatment which seems to offer some hope for recovery, every effort should be made to diagnose this type of infection.

TREATMENT

The basic treatment for actinomycosis is rest in bed and good food, supplemented by vitamin therapy and, under special conditions, natural or artificial irradiation. Next in importance is surgery. Adequate drainage is essential; all sinus tracts should be explored and drained and as much of the severely damaged

tissue excised as practical. Pleural lesions require surgical drainage, but usually pulmonary lesions drain through the bronchi. Lobectomy will probably be used in selected cases which have resisted other types of treatment.

Among the various supplementary methods of treatment, potassium or sodium iodide, thymol, X-ray and radium have been most frequently employed.

The iodides are of enough value to justify their use in almost every case of actinomycosis, but they are not nearly as effective as in some of the other mycoses; and when used alone, they are often entirely ineffective. Using a saturated solution of potassium iodide, the initial dose should be 5 drops t.i.d., and this should be increased by either one drop each day or one drop for each dose per day up to 20 or 30 drops per day. As much as 4 or 5 g. have been given daily for a period of months. Usually it is advisable to stop increasing doses at 20 drops t.i.d. and to start over immediately with 5 drops t.i.d. If patients develop sensitivity, the drug should be discontinued unless the reaction has subsided and then started again at the initial dose. Sodium iodide in doses of 1 g. may be given once or, at most, twice each day.

Thymol may be given by mouth in daily doses of 1 g. or 3 doses of 0.5 g. Although a number of successful results have been reported with thymol therapy, there have also been many failures. In our experience, it has been no better than iodides and much less effective than the sulfonamides.

X-ray, and to a lesser extent radium, is often very effective treatment as a supplement to surgery and iodides. The doses should be carefully regulated by an expert roentgenologist.

Sulfanilamide was used by Walker (28) in England and by Bailey (2) in this country in 1938. Ten successful reports (5, 6, 9, 10, 14, 19, 20, 22, 23, 25, 29) and only one failure have appeared in the literature since 1938. It is interesting that the one reported failure with sulfanilamide later responded satisfactorily to treatment with thymol (6). Hemmens and Dack (15) succeeded in curing with sulfanilamide rabbits experimentally infected with *Bacterium necrophorum* which is rather closely related to actinomyces. Mitchell (21) reports the cure of one case of actinomycosis with sulfapyridine.

Cutting and Gebhardt (8) found in 1941 that sulfadiazine and sulfathiazol were more fungistatic than sulfanilamide for both the aerobic and the anaerobic types of actinomyces. Sulfanilamide, sulfapyridine, sulfathiazol and sulfadiazine have all been used in the Duke Clinic as a part of the treatment for actinomycosis caused by *Actinomyces bovis*. At the present time sulfadiazine seems to be the drug of choice although the newer sulfamerizine has the theoretical advantages of slower absorption and excretion and is less likely to crystallize out in the kidneys.

As soon as the diagnosis is established, we start treatment with one of the sulfonamides, and surgical drainage is carried out while the patient has a sulfonamide level in the blood of 4 to 6 mg. per cent. After the acute effects of the operation are over, potassium iodide is started at the usual dose of 3 drops t.i.d. and increased daily as described above. We have maintained a blood sulfonamide level of 5 to 10 mg. per cent for a period of four to six months. After the patient is "apparently well," the drug is discontinued; but if symptoms recur, it is started

again and new foci, if present, are drained. X-ray is used as a stimulus to indolent lesions whether external or internal.

The sulfonamides do not give results in actinomycosis analogous to those observed in pneumococcus pneumonia or meningococcus meningitis. Although temporary improvement nearly always follows their use, we have seen several cases of the anaerobic type where the disease again became progressive and resulted in death.

Actinomycosis is a chronic disease with remissions, spreads and generalized dissemination analogous to tuberculosis. Patients should be observed for a period of years rather than months before being classified as cured.

SUMMARY

Approximately 90 per cent of the clinical cases of actinomycosis are caused by *Actinomyces bovis*. Beginning in 1938, 13 reports have appeared in the literature indicating that the sulfonamides are very effective in the treatment of this disease. In most instances the sulfonamides were given along with potassium iodide.

The remaining 10 per cent of cases of clinical actinomycosis are caused by aerobic *Actinomycetes* or *Nocardia*. Some of these *Nocardia* are acid-fast or partially acid-fast. Twenty-six cases of pulmonary infection with the acid-fast type have been collected from the literature. The mortality is high: 25 of the 26 cases were dead at the time the reports were published. Two new cases of pulmonary and chest wall infections with acid-fast *Nocardia* are added in this report. Excellent results were obtained with rest treatment, surgery, vitamins, sulfonamides and iodides. The patients are apparently cured.

SUMARIO

Aproximadamente 90 por ciento de los casos clínicamente de actinomicosis son ocasionados por el *Actinomyces bovis*. A partir de 1938, 13 comunicaciones que han aparecido indican que los sulfonamidos son muy eficaces en el tratamiento del mal, habiéndose administrado en la mayoría de los casos junto con yoduro potásico.

El 10 por ciento restante de los casos clínicamente de actinomicosis son causados por *Actinomycetes* aerobios o *Nocardia*. Algunas de estas *Nocardia* son completa o parcialmente ácidorresistentes. De la literatura se han compilado 26 casos de infección pulmonar por el tipo ácidorresistente. La mortalidad es alta: 25 de los 26 enfermos y habían muerto para la fecha en que se publicaron las comunicaciones. En esta comunicación aparecen dos nuevos casos de infecciones del pulmón y de la pared torácica por *Nocardia* ácidorresistentes, habiéndose obtenido en ellos excelentes resultados con el reposo terapéutico, la cirugía, las vitaminas, los sulfonamidos y los yoduros, y hallándose los enfermos aparentemente curados.

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ATYPICAL PNEUMONIA SIMULATING PULMONARY TUBERCULOSIS

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For many years it has been the teaching of the medical profession to view a patient, subacutely ill, with roentgenological evidence of infiltrations in the upper lung fields, as probably tuberculous, unless proved otherwise. Schlack (1), in reviewing 100 cases of nontuberculous lesions diagnosed as tuberculosis, gives the breakdown of final diagnoses. In order of frequency, bronchiectasis, asthma, pulmonary cancer, pneumonoconiosis, cardiac hypertrophy and pulmonary abscess accounted for 90 per cent of the cases.

In recent years it has become apparent that atypical pneumonia can produce lesions, which at times are indistinguishable from pulmonary tuberculosis. This has been noted and reported in the literature on several occasions. Campbell *et al.* (2), in a review of a series of 200 cases of atypical pneumonia, of which 23, or 11 per cent, were upper lobe lesions, had 5 of these misdiagnosed as pulmonary tuberculosis. Crow (3) reported a case admitted to a sanatorium with a diagnosis of tuberculosis of the right upper lobe, the diagnosis being made on one roentgenogram. The lesion cleared up completely in two weeks, proving the diagnosis to be inaccurate. Kneeland and Smetana (4) report one of their cases in which pneumothorax was instituted, only to discover it to be an atypical pneumonia at a later date. In a clinical review of 96 cases of atypical pneumonia at this Station, of which 7 had upper lobe involvement, the roentgenological diagnosis in 2 was pulmonary tuberculosis (5). Conversely, we have had one case diagnosed as atypical pneumonia which later proved to be tuberculosis (case 3).

With the apparent increase in the incidence of atypical pneumonia, and especially since the profession is becoming diagnostically more conscious of this entity, it is evident that differential diagnostic criteria should be promulgated to avoid mistakes in diagnosis. It is the purpose of this paper to present some of our observations, which may be of value in the differential diagnosis of these two conditions.

CLINICAL OBSERVATIONS

The symptoms and clinical signs of atypical pneumonia have been adequately and completely described in the current literature (6). The usual gradual onset of the disease, associated with malaise, generalized aches and pains, dry, nonproductive cough and fever, may be simulated by any case of acute pneumonic tuberculosis. Our experience has been that a differential diagnosis cannot be made definitely on the basis of the history and physical examination. Where serial roentgenograms are not feasible, the persistence of cough and expectoration, plus the finding of râles for a period greater than twenty-one days from the onset of the disease, even though clinically and symptomatically the patient appears to be much improved, should lead one to suspect tuberculosis.

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ROENTGENOLOGICAL ASPECTS

In reviewing our 7 cases of upper lobe atypical pneumonia roentgenologically we found two types of shadows. The most common finding was an increase in the bronchial markings, manifested by linear streaking densities with superimposed mottled shadows. This process was found to be most marked at the hilum and, with an extension of the disease, would spread fan-like outward from the hilum toward the periphery of the lung fields. The other type of finding was an area of increased tissue density in the parenchyma of the lung, relatively uniform throughout and resembling the shadow seen in early pleural effusion. Campbell *et al.* (2), discussing the physiopathology of atypical pneumonia, believe the disease is essentially a peribronchitis, a peribronchiolitis, bronchitis and bronchiolitis, with plugging of the bronchi and bronchioles, resulting at times in a patchy atelectasis. Roentgenographically, we find the criteria of atelectasis to be present in some of our cases, that is, shifting of mediastinal structures and narrowing of intercostal spaces. However, in only 2 of our 7 cases were the entire right upper lobes involved, and it is our experience that when only part of a lobe is involved concomitant evidence of atelectasis is absent. Complete involvement of an upper lobe in atypical pneumonia usually will reveal some associated evidence of atelectasis, whereas in complete consolidation of a lobe due to pneumonic tuberculosis, this is usually not the case. Because of the fact that there was such a wide divergence of roentgenological findings in our cases of atypical pneumonia, that is, one case would have involvement of an entire lobe with atelectasis, in another case the lesion consisting of mottled densities would be confined to one or two interspaces with or without hilar involvement, in still another the findings would be those of a uniform tissue density, it was felt that we could not make a definite differential diagnosis from a single roentgenogram. In serial roentgenographic studies of our cases, it was observed that we could expect our atypical pneumonia to show complete clearing of chest involvement in from a minimum of four to a maximum of twenty days. As a general rule, if the serial roentgenograms still reveal a density at the end of twenty days following the onset of the illness, pulmonary tuberculosis must be seriously considered, even though there may be other evidence, such as hilar involvement and atelectasis, to favor a roentgenological diagnosis of atypical pneumonia.

Several brief clinical histories and roentgenograms will serve to illustrate the discussion above.

CASE REPORTS

Case 1: R. F., a white soldier, twenty-seven years of age, was admitted to the hospital on May 21, 1942, with a one-day history of generalized aches and pains, headache, malaise, fever and chilly sensations. The physical findings on admission were normal, except for a moderate injection of the pharynx. Admission temperature was 100°F., pulse rate 82, respirations 20 per minute. The white blood cell count was 9,200, with 72 per cent polymorphonuclears. The working diagnosis was influenza. The patient continued to run a febrile course, reaching 103.8° F. on May 23, 1942. He also developed a nonproductive cough and physical examination of chest on May 25, 1942 revealed suppressed breath

sounds with an occasional fine moist râle in the right upper lobe. A roentgenogram taken the same day revealed complete consolidation of the right upper lobe (figure 1). A roentgenogram taken seven days later is of interest in that it shows almost complete clearing of the density. Fever persisted for eight days. The patient was treated symptomatically and made an uneventful recovery; he was discharged to duty on the twentieth hospital day.

This case illustrates the difficulty in making a definite diagnosis roentgenologically. Sputa were studied both for pneumococci and tubercle bacilli, with negative findings. The rapid clearing of the lesion ruled out tuberculosis and clinically this patient did not resemble a pneumococcus pneumonia. The string-like bronchial markings radiating from the hilar region are considered a criterion for a diagnosis of tracheobronchitis by Kornblum and Reimann (7).

Case 2: L. M. P., a white soldier, twenty-six years of age, admitted to the hospital September 1, 1942, with a two-day history of dry cough, generalized aches and pains, fever and chilly sensations. The physical findings on admission were normal, except for injection of the pharynx and bilateral varicosities of the legs. Admission temperature was 101°F., pulse rate 100, respirations 20 per minute. The white blood cell count was 6,800, with 64 per cent polymorphonuclears. The working diagnosis was influenza. Because of persistent, irritating dry cough, a roentgenogram of the chest was taken September 2, 1942 (figure 2). A roentgenogram taken fifteen days following onset of illness reveals complete clearing of the parenchymal lesions. The patient ran a febrile course for seven days, the temperature coming down by lysis. He made an uneventful recovery and was discharged to duty on the twenty-second hospital day.

When we saw the patient's first film (figure 2), the impression of a tuberculous lesion with cavitation was so strong that sputa and gastric studies were immediately ordered. All were negative and a roentgenogram taken two weeks later revealed the complete clearing of the right upper lobe. We frequently observed hilar densities concomitant with patchy parenchymal involvement, and we feel that this finding at times favors the diagnosis of an atypical pneumonia.

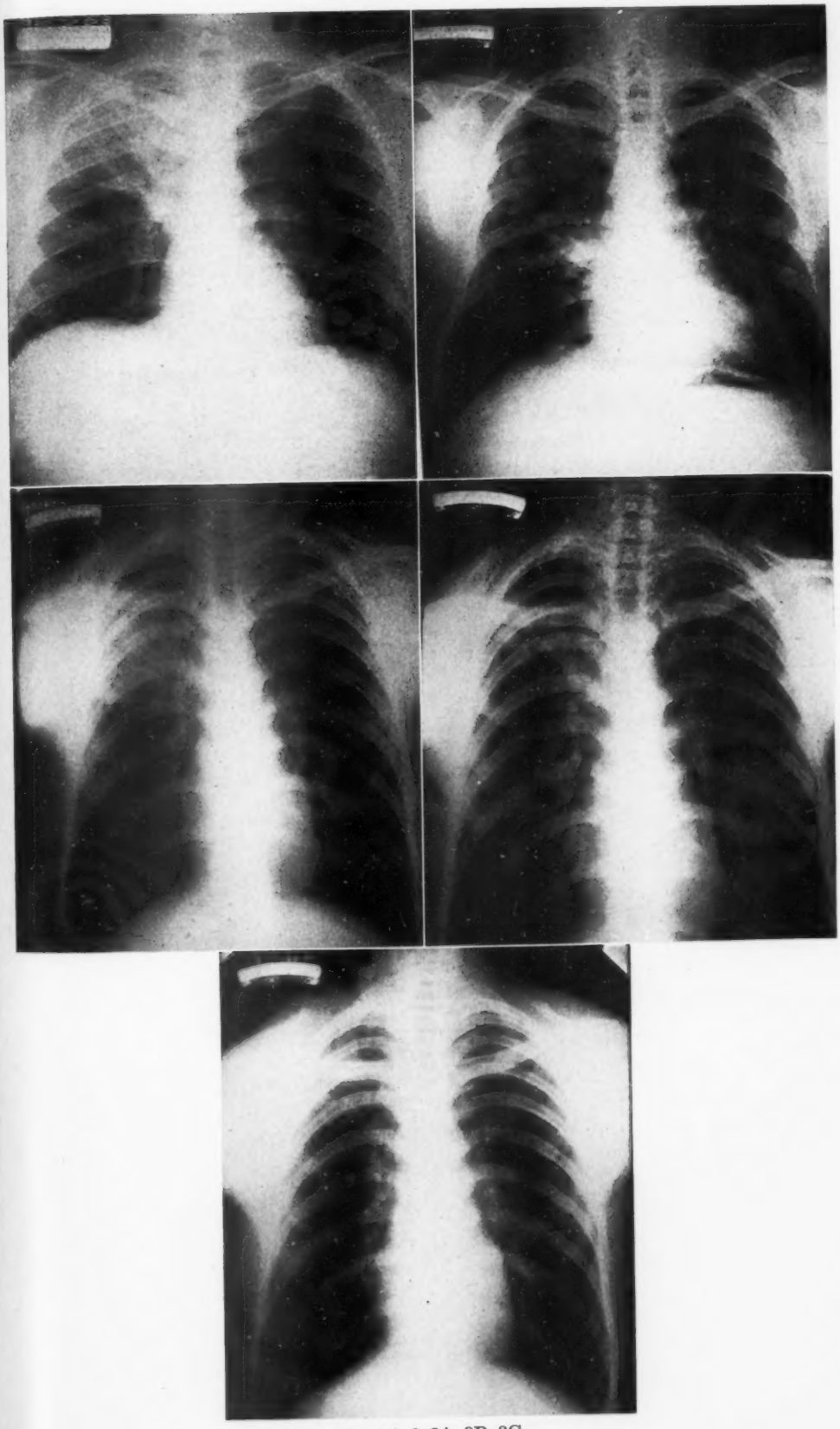
FIG. 1. (Upper left) (Case 1) Film taken on May 25, 1942, six days following onset of illness. Complete mottled consolidation of the right upper lobe with hilar involvement; also narrowing of the intercostal spaces and retraction upward of the minor fissure, denoting atelectasis of the right upper lobe.

FIG. 2. (Upper right) (Case 2) Film taken on September 2, 1942, four days following onset of illness. Marked increase in hilar shadow with scattered mottled densities throughout the right upper lobe. In the right second anterior interspace is a suspicious area of mottling with a central highlight suggestive of cavitation.

FIG. 3A. (Center left) (Case 3) Film of May 10, 1943 reveals a mottled consolidation, extending from the right hilum and involving the first and second anterior interspaces of the right upper lobe. Roentgenological diagnosis: Atypical pneumonia of the right upper lobe.

FIG. 3B. (Center right) (Case 3) Film of May 26, 1943 reveals some clearing as compared with previous film (figure 3A). Fibrous and mottled densities persist.

FIG. 3C. (Bottom) (Case 3) Film of July 3, 1943 shows fibrocaseous tuberculosis of the right upper lobe with several suspicious areas of cavities in the first and second anterior interspaces on the right.



FIGS. 1, 2, 3A, 3B, 3C

Case 3: J. H., a white soldier, twenty-two years of age, was admitted to the hospital on May 10, 1943, with a three-day history of generalized aches and pains, malaise, dry cough, fever and chilly sensations. The physical findings on admission were normal, except for a red and granular pharynx, diminished breath sounds and fine moist râles over the right upper lung field. Admission temperature was 100° F., pulse rate 110, respirations 20 per minute. The white blood cell count was 7,600, with 68 per cent polymorphonuclears, 26 per cent lymphocytes and 6 per cent monocytes. The working diagnosis was atypical pneumonia of the right upper lobe. A roentgenogram taken on the day of admission confirmed the diagnosis (figure 3A). The patient had a low grade febrile course for eight days following admission. He appeared clinically and symptomatically to be much improved, despite the persistence of physical signs in the right upper lobe. On the eleventh hospital day, another roentgenogram was taken. There was evidence of some clearing of the pneumonic process. It was felt, however, that in spite of the clinical improvement of the patient the persistence of physical signs in the chest and the slow clearing of the chest involvement as shown in the roentgenogram were not usual for atypical pneumonia. Sputum studies for tubercle bacilli were begun and on the thirteenth hospital day a positive sputum was reported. The diagnosis was confirmed by repeated positive sputa and by guinea pig inoculation. Figure 3B illustrates the fibrous and mottled densities in the right upper lobe on the sixteenth hospital day. The majority of atypical pneumonias will show complete clearing by this time. Figure 3C reveals a fibrocaseous tuberculosis with several suspicious areas of cavitation in the first and second anterior interspaces. Sputa were still positive at this time.

SUMMARY

1. Atypical pneumonia may simulate pulmonary tuberculosis both clinically and roentgenographically, and the reverse is true.

2. Approximately 7 to 10 per cent of atypical pneumonias have upper lobe involvement, which is the usual site for pulmonary tuberculosis.

3. Serial roentgenograms showing apical lesions failing to clear in twenty days, following the onset of the disease, should raise the suspicion of pulmonary tuberculosis.

4. Sputum studies for tubercle bacilli are indicated in all doubtful cases.

5. If lesions persist for twenty days from the onset of the illness, and routine sputum studies are negative, further studies should be done, that is, sputum and gastric concentrates, and guinea pig inoculation.

6. Because of the apparent increase in the incidence of atypical pneumonia, the need for an early differential diagnosis is imperative.

SUMARIO

1. La neumonía atípica puede simular tuberculosis pulmonar, tanto clínica como roentgenográficamente, y lo contrario es también cierto.

2. Aproximadamente de 7 a 10 por ciento de las neumonias atípicas muestran invasión del lóbulo superior, el cual constituye el asiento habitual de la tuberculosis pulmonar.

3. Los roentgenogramas seriados que revelan lesiones del vértice que no desaparecen en un plazo de 20 días, después de la iniciación del mal, deben avivar la sospecha de una tuberculosis pulmonar.

4. En todo caso dudoso estaán indicados estudios del esputo en busca de bacilos tuberculosos.

5. Si las lesiones perduran 20 días después de la iniciación de la enfermedad y los estudios habituales del esputo resultan negativos, deben realizarse otros nuevos, es decir, del esputo concentrado, de lavados gástricos e inoculación en el cobayo.

6. Debido al aparente aumento en la fecuencia de la neumonía atípica se impone el diagnóstico diferencial temprano.

Grateful acknowledgment is made for the assistance of 1st Lieutenant John C. Baucom, Base Photographic Officer, and Technical Sergeant Antonio J. Abbadessa, both from the Base Photographic Section, Moody Field, Georgia, who made the photographs from the roentgenograms to illustrate this paper.

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"SPEED OF REACTION" HYPOTHESIS

Its Numerical Foundations in Respect to the Tubercle Bacillus

HIBBERT WINSLOW HILL[1]

Herein is given certain new material relating to an hypothesis more fully detailed in a serial (12 installments) published 1941 to 1943 by the British Columbia Provincial Board of Health, Victoria, B.C. (1); and presented (in abstract) for the writer by Dr. A. J. Chesley, at the 18th annual meeting of the American Epidemiological Society, New York City, April 25, 1941.

For reference to the cognate general literature, see above serial (*The Epidemiology of "Human" Bacillus Tuberculosis in the Human*).

The material herewith is intended to further elucidate the above hypothesis concerning an old and very familiar question in regard to human tuberculosis; which question may be set forth briefly as follows.

THE QUESTION

The first infection of humans with living virulent human type tubercle bacilli sets up numerous tissue changes, the first change specifically recognizable being a positive tuberculin reaction.

These tissue changes as a whole may end ultimately in any one of three very different main outcomes, which may be stated broadly as:

A: No material damage at any time.
B: Material damage, variable as to clinical manifestations and duration, but ending in more or less permanent recovery.
C: Material damage, also varying as to clinical stages and duration, but ending finally in death.

No epidemiological or clinical observation in human tuberculosis is more widely or better attested than the above—that is, than the existence of these three subdivisions (classes *A*, *B* and *C*) of the total human type tubercle bacillus infectees.

Moreover, it is obvious that, regardless of what may eventually prove to be the exact current relative proportions which these three classes of human tubercle infectees may respectively bear to the total current human tubercle infectees, the same familiar question inevitably must recur—what factor or factors function in deciding, for each individual human infectee, which of these three well established main outcomes he will be finally found to have yielded?

Although, then, the relative proportions which classes *A*, *B* and *C* may in reality present currently are not germane to the above question, yet by assigning to these three classes such approximate relative proportions as the best available evidence may suggest as now current, a rather more concrete visualization of the epidemiological picture may be had.

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As elsewhere derived (1), these relative proportions now appear to approximate (so far at least as concerns currently the North American whites of the United States and Canada) the general order of those values which follow:

Class *A* (no material damage) is then found to contain a large majority of the total human infectees (that is, persons infected with human type tubercle bacilli); this majority probably approximating about three-fourths (75 per cent) or so of the total infectees.

Class *B* (material damage, with recovery) then will present a small minority only of those total infectees; a minority approximating perhaps about one-sixth (17 per cent).

Class *C* (material damage, with death) will therefore show a still smaller minority of the total infectees, a minority approximating about one-twelfth (8 per cent).

Obviously, the figures suggested above for class *B* (one-sixth of the total infectees) and for class *C* (one-twelfth of the total infectees) imply that the much disputed case fatality of human tuberculosis amongst current North American whites probably approximates a figure not too far under or over about one-third (33 per cent) or so of the total cases (class *B* plus class *C*). Other estimates, however, of the total case fatalities of human tuberculosis have ranged from about one-sixth (17 per cent) of the total cases to about one-half (50 per cent) of them. But even such huge inexactnesses in the data cannot affect the main question—that is, why do these three classes, *A*, *B* and *C*, exist at all?

Since the comparison of two or more somewhat contrasting pictures aids in a clearer perception of each, comparable approximate figures are here added for human poliomyelitis and human pneumonic plague; also for virulent human type tubercle bacillus infections in guinea pigs. The figures given express approximations only to current conditions.

	TOTAL HUMAN TUBERCLE INFECTEES	TOTAL HUMAN POLIOMYELITIS INFECTEES	TOTAL HUMAN PNEUMONIC PLAGUE INFECTEES	TOTAL GUINEA PIG INFECTEES WITH LIVING VIRULENT HUMAN TYPE TUBERCLE BACILLI
Class *A* (no material damage).....	75%	98 to 99%	0%	0%
Class *B* (material damage, with recovery).....	17%	A fraction of 1 to 2%	0%	0%
Class *C* (material damage, with death).....	8%	A fraction of 1%	100%	100%
	100%	100%	100%	100%

From the foregoing tabulation it is clear that the question asked above in respect to human tuberculosis applies equally to human poliomyelitis also; that is, what factor or factors function to create the three classes *A*, *B* and *C*?

Note how conclusively this equal applicability of the same question to both

these infectious diseases (and to most others) shows that the relative proportions of classes *A*, *B* and *C* do not matter as regards this question; but only the existence of such classes, irrespective of their sizes.

These sizes are, however, of immense interest to the wider consideration of the natural history of the respective diseases concerned. But the present article relates only to the original question—how do these classes arise?

With reference to human pneumonic plague and tuberculosis in the guinea pig, the original question becomes—what factor or factors function to eliminate completely from these two diseases both classes, *A* and *B*—thus leaving these four diseases as presenting in common only class *C*.

AN ANSWER

To these questions an answer, the hypothesis already referred to, may here be recalled in outline.

All the epidemiological and clinical complexities above touched on may be reasonably well solved by postulating them as due to variations in the quantitative functioning of but one single factor, a factor qualitatively inherent in and common to all the infectees concerned.

For simplicity, the postulated operations of this factor are here described only insofar as concerns virulent human type tubercle bacilli infections of the human.

This factor is taken to be a genetic character which appears as merely one potentiality out of the very many thousand potentialities which the tissues of each new-born child possess at birth—and is that particular potentiality which alone can respond with specific immunity to the specific immunity-eliciting stimuli of the human type tubercle bacillus—and probably to these particular stimuli only.

The term immunity is herein used in its most inclusive sense—as a short designation for the sum total of all those specific tissue activities which may be stirred up by a tubercle infection to oppose the specific inimical bacillus activities of that infection, whatever the detail of those specific tissue-opposition-activities may be—bacteriostatic, bactericidal, phagocytic, the neutralizing of toxic products or other.

Such very specific genetically derived potentialities, functioning similarly, are postulated also as to all the immunity-eliciting pathogens; differing from each other in being specific, as a rule, each one to its own one pathogen only.

This very specific human potentiality (for example, against the tubercle bacilli) is taken as practically constant in nearly all persons, concerning two of its features, that is, the quality and the ultimately obtainable amount of the specific immunity it can produce through its specific bacillus-stimulated activities; but it may differ markedly from person to person in respect to a third and apparently most important feature, namely, in "its speed of reaction;" that is, in the particular speed with which the individual specific potentiality, for example, against the tubercle bacillus, possessed by each person can respond with the required specific immunity, to the specific immunity-eliciting stimuli of the infecting bacilli.

The following considerations show how important, even controlling, as to the final outcome of tubercle bacillus infection this variety in speeds of immunity response would appear to be.

For it may safely be accepted that no naturally acquired exogenous infection of

humans with living virulent human type tubercle bacilli can consist of an initial dose so "large" (that is, containing so enormous a number of bacilli) as to effect by this single dose alone, without further multiplication, any material damage.

Hence the initial size of such an initial dose is not controlling as to the final outcome, although (see Illustrative Examples) later the initial size may affect the lengths of the incubation periods.

What really matters as to the final outcome is the size to which, by fission, the dose of infection, be it initially "large" or "small," may ultimately grow.

For on that "size to which it may grow" depends, *pari passu*, the size of the bacillus-output of pathogenetic substances; and, be it always remembered, the size also of the bacillus-output of immunity-eliciting stimuli.

This size to which any given initial dose may grow in the tissues must depend on three main features of its tissue environment; first, on the degree to which the bacilli find themselves fully "at home" in regard to moisture and food supply, temperature, oxygen tension, carbon dioxide tension, etc.; second, on the quality and the amount of the specific tissue-opposition their bacillus-activities may then encounter; but third, and especially, on how soon after fission begins this specific tissue opposition to the bacillus activities may become effective.

For any and all delay in the responses of the tissues with specific tissue opposition affords just so much more time during which the bacilli may, by fission, increase unopposed; and therewith increase *pari passu* their pathogenetic output also.

True, their output of immunity-eliciting stimuli will also increase *pari passu* with their multiplication; but all such stimuli will remain wholly unproductive of immunity, unless and until such time has elapsed as the tissues may require for response to them with the development of actual immunity.

Note that with regard to the acquisition of immunity, artificially or naturally, no point is better established than the constant existence of a very definite time-lag, be it "short" or "long," between any given specific immunity stimulus and the corresponding immunity response which that stimulus may evoke from the tissues.

It would appear rather evident that, but for the existence of such a time-lag, no immunity-stimulating pathogen could produce any material damage at all, since, if there were no such time-lag whatever, infection and the corresponding immunity production would be practically simultaneous.

Clearly, the particular length of the time-lag shown by a particular infectee is merely the concrete expression of, and chiefly or wholly depends on, the particular speed with which that particular infectee can respond with immunity production to the immunity-eliciting stimuli he receives from his infection.

It may therefore be accepted in respect to human tuberculosis that class *A* (no material damage) consists of those infectees whose respective time-lags, although varying in length somewhat from infectee to infectee, are all relatively short, or otherwise stated, whose respective speeds of reaction in immunity response are relatively fast; relative, that is, to the rate at which the bacilli may increase in number by fission.

These class *A* infectees are genetically fortunate in respect to tuberculosis in possessing these short time-lags (or, rapid speeds of reaction); for they therefore

are able to begin the cutting down of the bacillus activities relatively soon after fission begins; hence before the bacilli can attain to those enormous numbers (and corresponding pathogenetic outputs) which further unopposed fissions would otherwise yield. Thus the bacillus activities receive an early and thereafter constantly growing check which ends them before material damage is done. (See Illustrative Examples.)

Class *B* (material damage, with recovery) consists of infectees whose respective time-lags are somewhat longer (or whose speeds of reaction are somewhat slower) than those of class *A*. Hence the bacilli secure a greater number of unopposed fissions before effective tissue opposition can be brought to bear against them; meantime some material damage is assured; but again the thereafter rapidly growing tissue opposition finally quells the bacillus activities, and recovery follows.

Class *C* (material damage, with death) consists typically of infectees with still longer time-lags or still slower speeds of reaction than those of class *B*. Hence the bacilli (and their outputs), flourishing longer unopposed, make gains too great for the delayed tissue opposition to overtake—death resulting. Doubtless, however, some deaths in the course of tuberculosis are due rather to "accidents," such as the particular sites of lesions, delayed therapeusis, etc., see discussion elsewhere (1).

This applies also to human poliomyelitis. But with regard to human pneumonic plague and guinea pig tuberculosis, it would appear that extremely long time-lags or extremely slow speeds of reaction are chiefly responsible for practically all the deaths.

The hypothetical examples which follow here are offered only as "first approximations" and only as illustrating how quantitative variations in the single genetic factor above postulated (the speed of reaction of the tissues in immunity response) may work out numerically: (*1*) to achieve the very diverse final outcomes of infection; namely, *A*, no material damage; *B*, damage with recovery; *C*, damage with death; (*2*) to control, in conjunction with the initial size of the infecting dose, the lengths of incubation periods; (*3*) to provide at recovery a surplus of rather short lived immunity for future rather brief protection. Also, the above postulation reasonably accounts for: (*4*) the active minimal lesion which heals; (*5*) the promptness with which some class *B* infectees recover and the delay which others show; (*6*) the promptness with which some class *C* infectees die, and the lingering delay in the death of others.

Moreover, this postulated factor apparently may similarly operate *mutatis mutandis* in respect to all other immunity-eliciting pathogens, as well as for tubercle bacilli.

A number of other less direct correlations have been set forth elsewhere (1); and probably others remain as yet unidentified.

ILLUSTRATIVE EXAMPLES

In the guinea pig: In guinea pigs the speed of immunity response is practically zero; hence the size of the initial dose does not affect case occurrence, since a case

always develops in guinea pigs on infection with human type virulent tubercle bacilli, but it does affect the length of incubation period, the time interval between infection and first detectible damage.

Thus, let x be the number of human type tubercle bacilli in the initial dose. Assume that this x (unmultiplied) may produce in the tissues x units of damage, and x units of tissue-opposition-eliciting stimuli to such damage. Now in guinea pigs these stimuli are unproductive of immunity; not from any lack of the stimuli, but from practical lack of guinea pig response in the form of immunity to them. Hence the initial dose (x) multiplies "normally" in guinea pigs, practically without "immunity," that is, without restraint from specific guinea pig tissue opposition.

In due time, fission increases x bacilli to 2x bacilli. Let us call this time one fission period. Then we have, in guinea pigs,

Initial dose = x bacilli
Fission 1 = 2x bacilli
Fission 2 = 4x bacilli
Fission 3 = 8x bacilli
Fission 4 = 16x bacilli
Fission etc. = etc.

For example—Fission 10 = 1024x
Fission 20 = about 1,000,000x
Fission 30 = about 1,000,000,000x etc.

Hence tuberculous damage always occurs sooner or later (in guinea pigs); but how soon or late (that is, the length of the incubation period) depends on the size of x, the initial bacillary dose. Merely to have a figure for illustration, let us assume 1,000,000 bacilli are just enough to produce detectable beginnings of such damage. Then if x = 1, the time required for 20 fission periods will be the length of the incubation period. But if x = 1,000, 10 fission periods will suffice; that is, this latter incubation period will be only half as long as the first one (20 fissions) and so on.

In the human: However, in the human, the x immunity stimulus of an initial dose of x bacilli does elicit a specific tissue-opposition response sooner or later; how soon or late determines whether a case occurs, or not—and, together with the size of the initial bacillary dose, sets the length of the incubation period, if any.

Example I

If the full immunity response to x stimuli were truly immediate (as it probably never is) the initial dose (x bacilli) would at once be put out of action by x immunity. This may be expressed as x bacilli opposed by x immunity = 0; no fission occurring and no damage developing in the tissues.

Example II

If the immunity response lags somewhat, as apparently it always does, let this lag be such that the response occurs just after fission 1. Then the initial dose of

x bacilli becomes, by fission 1, 2x bacilli; but 2x bacilli, in the presence of x immunity (from the initial dose) leave only x bacilli to multiply (2nd fission) = 2x bacilli. The first fission product (also 2x bacilli) has by now induced 2x immunity; hence, 2x bacilli opposed by 2x immunity = 0 bacilli left active.

Example III

If the immunity response lags to just after fission 2, the initial dose of x bacilli becomes, by fission 1, 2x bacilli, and by fission 2, 4x bacilli; but x immunity (from the initial dose) now reduces this 4x bacilli to 3x bacilli. Fission 3, therefore, produces 6x bacilli.

This 6x bacilli of fission 3 encounters then 2x immunity (from fission 1); hence becomes 4x bacilli; and, on multiplication by fission 4, 8x bacilli. This 8x bacilli of fission 4 encounters 4x immunity (from fission 2), and so produces 4x bacilli to multiply; becoming (by fission 5) 8x bacilli. This 8x bacilli of fission 5 encounters 6x immunity (from fission 3) and is reduced to 2x bacilli. On multiplication this residual 2x bacilli becomes (by fission 6) 4x bacilli. This 4x bacilli of fission 6 encounters 8x immunity (from fission 4). Thus 4x bacilli opposed by 8x immunity = 0 bacilli left active; and there are 4x immunity units left over.

Example IV

If the response lags to just after fission 3, we have

Initial dose x bac.– 0x im. = x bac. to multiply; becomes 2x (fiss. 1)
Fiss. 1 gives 2x bac.– 0x im. = 2x bac. to multiply; becomes 4x (fiss. 2)
Fiss. 2 gives 4x bac.– 0x im. = 4x bac. to multiply; becomes 8x (fiss. 3)
Fiss. 3 gives 8x bac.– 1x im. (from init. dose) = 7x to mult. = 14x (fiss. 4)
Fiss. 4 gives 14x bac.– 2x im. (from fiss. 1) = 12x to mult. = 24x (fiss. 5)
Fiss. 5 gives 24x bac.– 4x im. (from fiss. 2) = 20x to mult. = 40x (fiss. 6)
Fiss. 6 gives 40x bac.– 8x im. (from fiss. 3) = 32x to mult. = 64x (fiss. 7)
Fiss. 7 gives 64x bac.– 14x im. (from fiss. 4) = 50x to mult. = 100x (fiss. 8)
Fiss. 8 gives 100x bac.– 24x im. (from fiss. 5) = 76x to mult. = 152x (fiss. 9)
Fiss. 9 gives 152x bac.– 40x im. (from fiss. 6) = 112x to mult. = 224x (fiss. 10)
Fiss. 10 gives 224x bac.– 64x im. (from fiss. 7) = 160x to mult. = 320x (fiss. 11)
Fiss. 11 gives 320x bac.–100x im. (from fiss. 8) = 220x to mult. = 440x (fiss. 12)
Fiss. 12 gives 440x bac.–152x im. (from fiss. 9) = 288x to mult. = 576x (fiss. 13)
Fiss. 13 gives 576x bac.–224x im. (from fiss. 10) = 352x to mult. = 704x (fiss. 14)
Fiss. 14 gives 704x bac.–320x im. (from fiss. 11) = 384x to mult. = 768x (fiss. 15)
Fiss. 15 gives 768x bac.–440x im. (from fiss. 12) = 328x to mult. = 656x (fiss. 16)
Fiss. 16 gives 656x bac.–576x im. (from fiss. 13) = 80x to mult. = 160x (fiss. 17)
Fiss. 17 gives 160x bac.–704x im. (from fiss. 14) = 0x bac.—and a surplus immunity of 544x units; (i.e. 704–160). But note that further "over-immunity" will arise later, from the immunity-eliciting stimuli of the bacilli of fissions 15, 16 and 17 which give 2,128x units of "over-immunity" in all. (And similarly in example III.)

Simple inspection of example IV shows that, if x = 1, the number of 1,000,000 bacilli assumed to be necessary for case development is not attained. If x = 1,400, the number of 1,000,000 bacilli and the beginnings of damage appear at fission 15, but the bacilli disappear at fission 17, leaving surplus immunity, the net result to be expressed in the clinical sense as an active minimal lesion, promptly healing. If x = 4,500 bacilli, the 1,000,000 bacilli will appear at about

fission 10. If x = 25,000 bacilli, the 1,000,000 will develop about at the time of fission 6. But note that whatever be the value of x, all bacillus activities disappear at fission 17.

By comparing example IV with the guinea pig schedule above, the effect of the immunity time-lag plus the size of the dose can be seen.

If the immunity response be delayed to just after the fourth fission (that is, when 16x bacilli have developed) the figures become less readily graspable, but it would appear that, as the time-lag in immunity response increases, a point is reached where the bacilli will gain faster than the thus delayed immunity gains. Loss of bacilli in the discharges will help this situation. See Installment 4, of (1).

These illustrative examples constitute, at best, only "first approximations." Many questions arise; for example, do the fission periods, in tuberculosis, vary in length from day to day? Probably they do, dependent on variations in the local nutrition available to the bacilli, variations in oxygen supply, carbon dioxide tension, etc. (as in pneumothorax?)—this giving rise to some of the variations in the clinical condition of the patient.

OVER-REACTION OF THE TISSUES

If, in reality, the tissues over-respond with immunity, to the immunity-eliciting stimuli, let x bacilli induce, not merely x immunity, but for illustration only, 10x immunity. Thus modified, fission 3 (example IV) becomes 8x bacilli − 10x immunity, or 0 bacilli left active; and 142x of surplus immunity.

If, however, the time-lag now be taken to extend to just after fission 10, the latter will show 1,024x bacilli; and, for fission 11 (1,024 − 10) 2 = 2,028 bacilli; and so on—that is, fission 17 will yield about 120,000x bacilli, fission 20 about 1,000,000x bacilli.

The powerful influence of the time-lag factor becomes thus very apparent.

SUMMARY

The essential dependence, of each of the three possible outcomes of invasion of the human by the tubercle bacillus, upon the factor of "speed of reaction" is illustrated by examples numerically expressed. Absence of material damage to an infectee, or material damage followed by more or less permanent recovery, or damage ending finally in death, may be explained by assuming quantitative variations in the functioning of a single factor common to all infectees. The factor is apparently a genetic character, specific throughout life with respect to tissue activities roused by infection by the tubercle bacillus. While this factor appears to be practically constant in respect to quality and amount of specific immunity produced, there is marked individual variation in the speed of the elicited reaction from person to person. It is not the size of the initial dose that matters so much as the size to which by bacillary fission the initial dose of infection may ultimately grow.

This ultimate size will depend especially upon how soon after fission begins in the initial dose the specific tissue resistance process becomes effective in opposing bacillus activities.

The time-lag between bacillary invasion and tissue response is the particular

factor dealt with in four illustrative numerical examples which are offered as first approximations typical of clinical experience with tuberculosis in the human.

SUMARIO

Por medio de ejemplos numéricamente expresados pónese de manifiesto la dependencia esencial en que se encuentran los tres posibles resultados de la invasión humana por el bacilo tuberculoso, del factor "velocidad de la reacción." Cabe explicar la falta de lesiones importantes en un infectado o la presencia de lesiones importantes seguidas de una reposición más o menos permanente, presuponiendo la existencia de variaciones cuantitativas en el funcionamiento de un solo factor que afecta en común a todos los infectados. Ese factor es aparentemente de naturaleza genética, y específico durante toda la vida con respecto a las actividades histológicas avivadas por la infección por el bacilo tuberculoso. Aunque dicho factor parece ser prácticamente constante en cuanto a la calidad y cantidad de la inmunidad específica que produce, existe decidida variación individual en la reacción provocada en distintas personas. El tamaño de la dosis inicial no es tan importante como el tamaño que puede alcanzar la misma mediante la fisión bacilar.

Dicha dosis final dependerá especialmente de la rapidez con que, después que comience la fisión de la dosis inicial, cobre eficacia el proceso específico de resistencia de los tejidos para oponerse a la acción del bacilo.

El tiempo transcurrido entre la invasión bacilar y la reacción histológica constituye el factor considerado en cuatro ejemplos numéricos que se ofrecen como las primeras aproximaciones típicas de la experiencia clínica con la tuberculosis humana.

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INFLUENCE OF ENVIRONMENTAL FACTORS ON FEVER IN PULMONARY TUBERCULOSIS [1, 2]

JOHN S. HOWE[3] AND ALVIN MAYNE

Although fever plays an important rôle in the diagnosis and prognosis of pulmonary tuberculosis, few statistical studies have been carried out on the nature of fluctuations in body temperature. Seasonal influence on the course of tuberculosis has been long known; Hippocrates (1) noted that the spring and fall were of greatest danger.

"Many cases (consumption) began in the winter and of these several took to their bed, though some went about without doing so. Early in spring most of those who had gone to bed died, while none of the others lost their coughs, though it became easier in the summer. During autumn all took to bed and many died."

Mills (2) in his study of tuberculosis deaths by month of onset showed that if the onset occurred in April the average duration was about fourteen months while for summer onset the average duration was twenty-five months. His statistics tend to confirm quite well the observations of Hippocrates.

Clayson (3) found in his study of temperature records at Edinburgh that definite increases in the number of high temperatures occurred during the spring months, March being the peak month. The effect of meteorological episodes upon the fluctuations in body temperature of patients with various types of tuberculosis has been analyzed by Petersen and coworkers (4) and by Pottenger (5).

Clinicians have noted tendencies for the entire population of a sanatorium to show parallel movements in temperature from day to day. It is the purpose of this study to evaluate these movements in a sanatorium group by statistical analysis and to determine possible relationships with environmental factors.

DATA AND METHODS OF STUDY

The records of the Edward Sanatorium at Naperville, Illinois were made available to us through the courtesy of the Medical Director, Dr. Jerome Head, and the Board of Trustees. This is a sanatorium of 101 beds and 207 admissions yearly, treating all types of pulmonary tuberculosis, with a considerable percentage of the patients receiving some form of collapse therapy. The average duration of sanatorium treatment is about six months. During the period of study the census varied from a low of 68 patients to a high of 96 patients.

Data were available extending over a period of fourteen months from November 14, 1938 to January 20, 1940, giving the daily number of patients whose oral

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[2] Read by title before the American Association of Pathologists and Bacteriologists, New York, April 10, 1941.

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temperature at any one of the three daily readings (at 8:00 a.m., 4:00 p.m. and 8:00 p.m.) was 99° F. or higher. For the purpose of our analysis these patients will be considered febrile. Further data were available in the form of a daily census of the number of patients in the sanatorium.

Variations present in the number of febrile patients in the sanatorium may be analyzed into the following classifications:

1: Variation caused by changes in the total number of patients in the sanatorium.
2: Secular or long-run shifts introduced by changes in the type of patient and the type of treatment.
3: Seasonal variations.
4: Possible weekly variations due to visiting days, operating days and other routines recurring at weekly intervals.
5: Possible irregular short-run changes due to the meteorological environment.

It is the primary purpose of this paper to investigate the effects of the meteorological environment. Other possible sources of variation have been treated largely with the view of obtaining the maximum possible homogeneity in the day-to-day variations.

By expressing the number of febrile patients as a percentage of the total number of patients in the sanatorium on the same day, variation resulting from the size of population will be readily eliminated.

Analysis of long-run variability caused by changes in the type of patient and of treatment presents obvious difficulties and cannot be undertaken in this paper. For our purposes it will be necessary to assume that the population of a sanatorium is homogeneous from week to week with respect to the tendency to be febrile under similar conditions for the period of observation. We recognize that this assumption is open to doubt. It is quite probable that the late spring and early summer rise in general febrile levels is associated with the admission of a large number of patients with active tuberculosis. This influx could definitely alter the curve.

LONG TERM AND SEASONAL TRENDS

In order to minimize the daily variations, the percentage of febrile patients was averaged by weeks and these data charted for the fourteen-month period. Chart 1 shows the result (upper curve) superimposed on a curve showing the weekly average mean temperature calculated from the records of the Chicago Weather Bureau. The dotted line (upper curve) is a free-hand curve smoothing the variations and showing the general trend.

It will be noted that the percentage of febrile patients rises rapidly beginning in early April to reach a peak in late May, which is then maintained until early July. The curve then falls rapidly until late August, when there is a sharp secondary rise continuing into September, followed by a second fall and another rise persisting through October. This curve for the percentage of febrile patients is in agreement with the spring activation of tuberculosis noted by observers from the time of Hippocrates.

If we compare the mean environmental temperature (lower curve), we find a

similar trend, but the rise in percentage of febrile patients precedes that in the mean temperature, the peak occurs earlier and the fall precedes the fall in mean temperature by about two months. Therefore, it appears that this seasonal trend, while roughly resembling the mean temperature curve, is not a simple effect of higher environmental temperature. It seems more likely that it merely reflects the tendency to spring activation and summer quiescence of tuberculous processes.

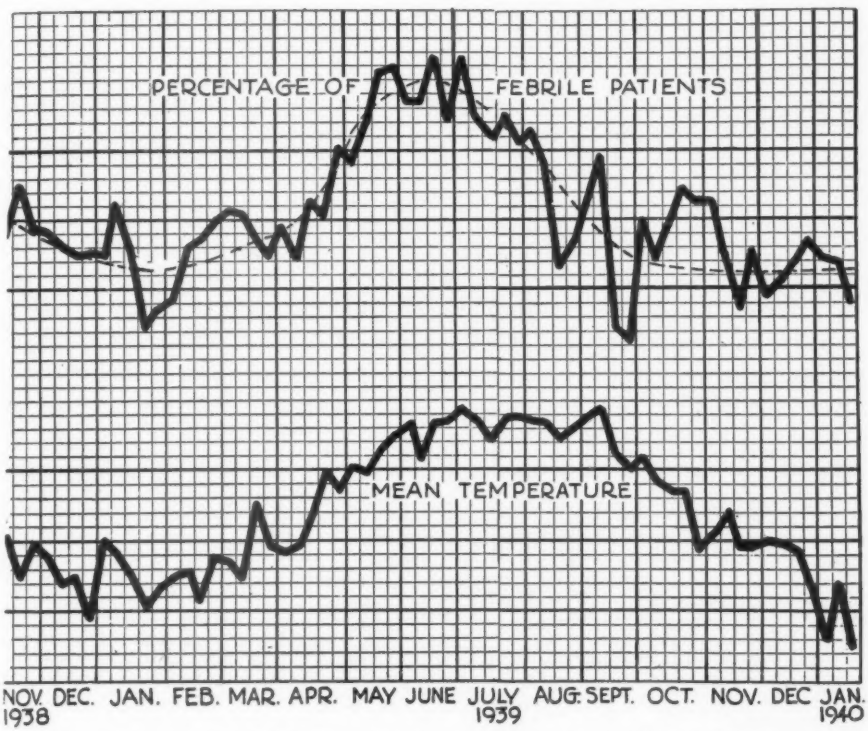
PERCENTAGE OF FEBRILE PATIENTS
MEAN TEMPERATURE
NOV. DEC. JAN. FEB. MAR. APR. MAY JUNE JULY AUG. SEPT. OCT. NOV. DEC JAN.
1938
1939
1940

CHART 1. Percentage of febrile patients and mean temperature. Weekly averages November 1938—January 1940.

DETERMINATION OF WEEKLY CYCLE

Examination of the data revealed a definite tendency to peaks on certain days which suggested a weekly cycle. Accordingly a corrected weekly index was calculated, which eliminated the long seasonal movements by computing the ratio of each day to the thirteen-day moving average.[4]

[4] A moving average is obtained by computing a series of averages using successive and overlapping groups of observations. A thirteen-day moving average is the series of averages obtained by totaling the first thirteen daily observations and dividing by thirteen, then totaling the observations from the second day to the fourteenth, inclusive, and dividing by thirteen. Similarly the third average is obtained by totaling the observations on the third to fifteenth day, inclusive, and so forth. The computation of such averages produces a series which is relatively smoother than the original observations and will remove entirely the presence of short cycles which may be present in the data.

Chart 2 shows the values for all Saturdays and Sundays compared to an average or "normal" and to the thirteen-day moving average. It is apparent that the ratio for Sundays is consistently above normal, while that for Saturdays is consistently below normal. Another feature noted is the slight shift in the level of Sunday from the winter to the summer months. To further analyze this difference, a weekly index was calculated for each month.

Chart 3 shows this index for January and July. Both winter and summer cycles show definite peaks in the percentage of febrile patients on Wednesday and Sunday. In the winter, however, the height of the Sunday peak is almost

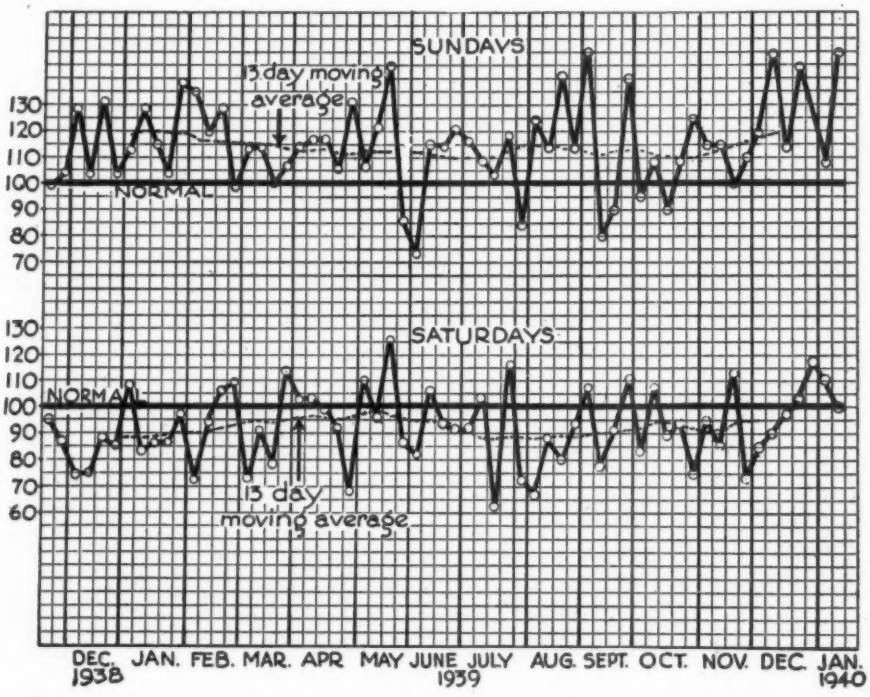

CHART 2. Ratio of percentage of febrile patients to thirteen-day moving average—comparison of Sundays and Saturdays

twice that of the Wednesday peak. In the summer the Wednesday and Sunday peaks are of equal height. The other days of the week show no striking trends.

On examination of the sanatorium schedule, the reason for this striking weekly cycle seemed apparent. Wednesday and Sunday were the officially designated visiting days. The regular days for operative procedures were Tuesday, Thursday and Saturday. These were considered in relation to the weekly cycle on the theory that febrile peaks might be expected to follow the regular operative days. However no peak occurs on Saturday following the regular operative day on Thursday, which seems to rule out this explanation.

It is possible that the weekly cycle might be associated with underlying cycles in the weather of short duration. Abbott (6) has found a six-day and eighteen-

hour rainfall cycle in Washington, D. C. However, we believe that the most satisfactory explanation is that of visiting days. This association of febile peaks and visiting days will not be surprising to physicians working in sanatoria, since it is a clinical impression common to many of them, although to our knowledge it has not been previously established by statistical methods.

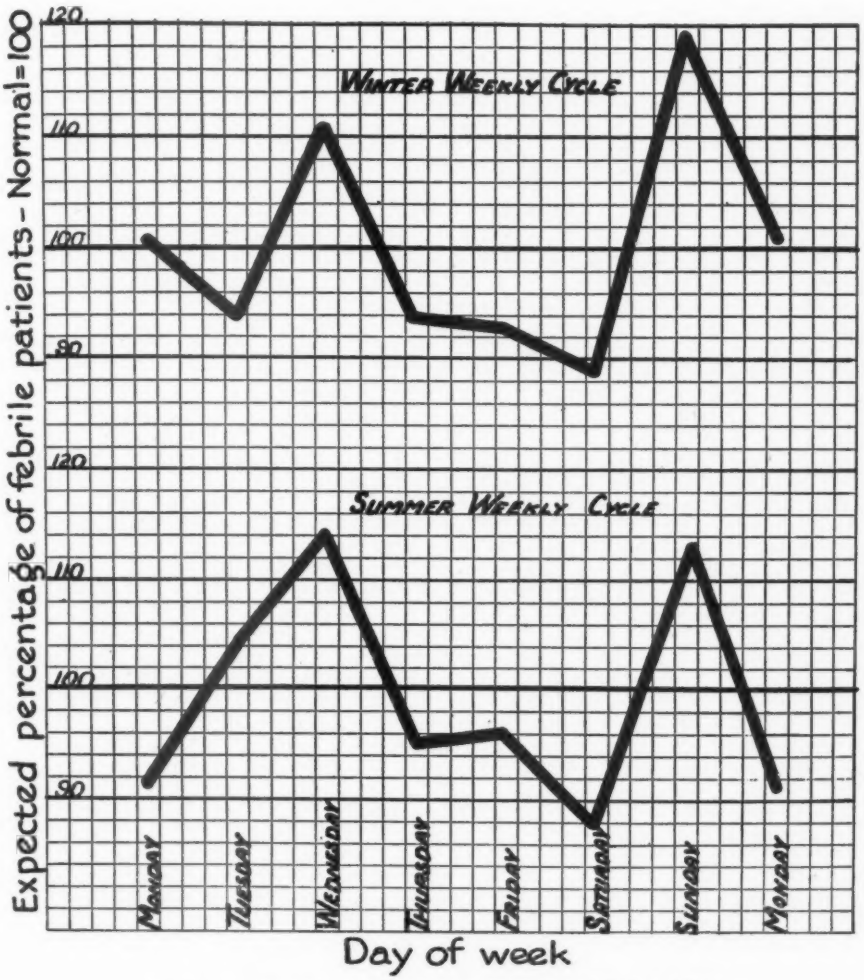

Chart 3. Weekly cycle in percentage of febrile patients

The difference between weekly cycles in summer and winter is less easily explained. Possibly it depends upon the fact that in the winter Wednesday is a less popular visiting day than in the summer, since most visitors must drive for some distance to reach the sanatorium. However, we have no data available on the actual number of visitors or the number of patients having visitors, so we cannot test this hypothesis by statistical methods.

DAILY VARIATIONS AND THEIR RELATION TO THE METEOROLOGICAL ENVIRONMENT

The removal of the seasonal cycle and the weekly cycle from the daily percentage of febrile patients left considerable variation, particularly during the summer months. The larger variations in the summer months as compared to the winter months led to the proposal of atmospheric temperature as a possible explanation.

Chart 4 shows the daily variations in the percentage of febrile cases and the daily deviations from normal temperature for two contrasting periods of the year, including three winter months and three summer months. The deviation from normal temperature as published by the U. S. Weather Bureau for Chicago was used as an index for atmospheric temperature.

During the months of December, January and February, very little association is to be noted between the mean temperature and the percentage of febrile patients However, during the summer months of July, August and September, the relationship is much closer, especially during the month of September. The difference in the association can reasonably be attributed to the difference in the degree of exposure to outside temperature. While no data on this question are available, it is known that during the winter the sanatorium has controlled temperature in the form of artificial heat, while during the summer the protection from outside temperature is not nearly as effective. The only winter month showing any sizeable correlation is January, but it is to be noted that January was exceptionally warm, averaging 7.7 degrees per day above normal.

Table 1 shows correlation coefficients for each month together with the average daily temperature in excess of normal. The comparison of the variance in the daily percentage of febrile patients for each month with the variance after the influence of temperature has been removed is also given. The contrast in the winter and summer months is seen in the size of the correlation coefficients during the different periods of the year. From May through October the correlation coefficient is relatively high, the lowest figure being +.58. During November the correlation drops off sharply and in April it becomes moderately high. A correlation coefficient of +.46 is obtained one per cent of the time whem sampling at random from a population with zero correlation, indicating that all the coefficients for the summer are significant.

Table 1 also shows that there is some correspondence between the variation in the correlation coefficient and the average size of the atmospheric temperature deviation for the month. The highest correlation is for September with +.81, the average temperature deviation being +5.1. The preceding month, August, showed an average atmospheric temperature deviation of +1.1 and the correlation coefficient was +.59. This association is even maintained for the winter months; in January the average atmospheric temperature deviation was +7.7 and the coefficient of correlation +.43.

As shown in column 3 of table 1, the variance during the summer months is generally higher than during the winter months. Column 4 gives the variance remaining after adjustment is made for variance attributable to seasonal and weekly cycles and atmospheric temperatures. It will be noted that the level of

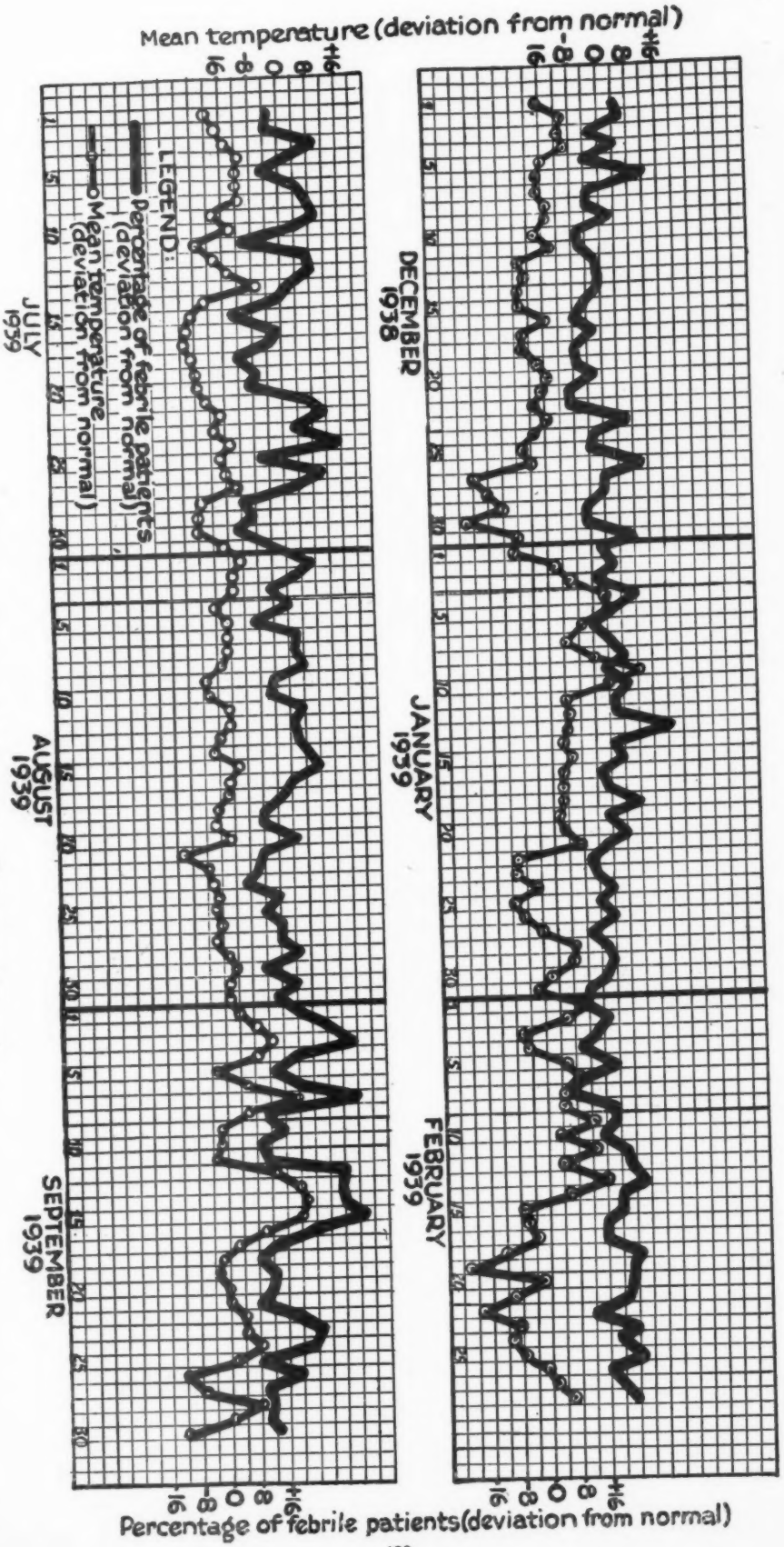

CHART 4. Percentage of febrile patients and mean temperature

variability as corrected (column 4) shows less difference between winter and summer months. The nature of the material is such that it is not possible to obtain an estimate of the size of the daily variation expected through chance.

The greater tendency to fever with high environmental temperature raises the question of whether this actually represents an unfavorable effect of heat on the tuberculous process. Mills (2) suggests that moist heat apparently has an unfavorable effect on tuberculosis. The statistical relationship here demonstrated might be interpreted as confirming his suggestion. On the other hand, the fact that the curve for percentage of febrile patients falls at least six weeks before the curve of environmental temperature indicates that the high environmental temperatures apparently do not cause an activation of the tuberculous

TABLE 1

Percentage of febrile patients—correlations with temperature; average temperature; variance, unadjusted and adjusted, by months*

MONTH	CORRELATIONS WITH TEMPERATURE DEVIATIONS	MEAN ATMOSPHERIC TEMPERATURE DEVIATION FROM NORMAL	VARIANCE OF DAILY PERCENTAGE OF FEBRILE PATIENTS, UNADJUSTED	VARIANCE OF DAILY PERCENTAGE OF FEBRILE PATIENTS, ADJUSTED*
1938				
December	+0.174	+0.42	38.36	28.87
1939				
January	+0.429	+7.71	34.89	18.42
February	+0.202	−0.71	31.68	22.46
March	+0.067	+2.84	12.60	16.18
April	+0.327	−1.70	36.30	22.06
May	*+0.643*	+3.87	89.22	32.46
June	*+0.670*	+3.43	104.16	51.02
July	*+0.634*	+1.64	70.63	35.83
August	*+0.588*	+1.06	57.54	17.08
September	*+0.808*	+5.10	99.75	28.19
October	*+0.637*	+1.93	45.81	32.20
November	−0.304	+2.97	26.66	21.18
December	−0.072	+7.82	26.73	17.18

* Adjusted for weekly, "seasonal," and temperature variations.

process. The autonomic lability of the tuberculous patient is well known and roughly analogous to that of the hyperthyroid patient, whose heat intolerance is universally recognized. It seems probable that this relationship with environmental temperature merely reflects the lability of the heat regulating mechanisms in tuberculous patients.

SUMMARY AND CONCLUSIONS

The daily percentage of febrile patients (oral temperatures of 99° of higher) in a tuberculosis sanatorium was studied over a fourteen-month period with the following results:

1. A seasonal variation of rather sizable proportions was found, with a peak in late May, June and early July.

2. A weekly cycle was observed with Wednesday and Sunday the peak days. These days correspond to the only two visiting days at the sanatorium.

3. A definite relationship between the atmospheric temperature and the day to day changes in the percentage of febrile patients was observed. This relationship was most marked in summer, when the patients were more directly exposed to changes in atmospheric temperature.

SUMARIO Y CONCLUSIONES

Durante un período de 14 meses se estudió en un sanatorio para tuberculosos el porcentaje diario de enfermos febriles (temperatura bucal de 37.2 o más) con el siguiente resultado:

1. Observóse una variación estacional de bastante intensidad, que alcanzó su cúspide a fines de mayo, y en junio y principios de julio.

2. Observóse también un ciclo semanal que alcanzaba sus cúspides los miércoles y domingos, días estos que representan los únicos dos en que se permiten visitas en el sanatorio.

3. Observóse una relación bien definida entre la temperatura atmosférica y el porcentaje de enfermos febriles, siendo más pronunciada en verano, en que los enfermos se encuentran más directamente expuestos a los cambios atmosféricos.

We wish to acknowledge with thanks the coöperation of Dr. Jerome Head, Medical Director, and the staff of the Edward Sanatorium.

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BASAL PULMONARY TUBERCULOSIS[1]

Results of Treatment

BURGESS L. GORDON,[2] ROBERT CHARR AND MARTIN J. SOKOLOFF

The purpose of the present communication is to report the results of treatment in a series of patients with basal pulmonary tuberculosis as compared with a group having upper lobe tuberculosis.

MATERIAL STUDIED AND FINDINGS

Between 1933 and 1943, in the Department for Diseases of the Chest of Jefferson Hospital and White Haven Sanatorium, 37 patients were treated for basal pulmonary tuberculosis. Of these, 30 were female and 7 male. Nineteen were in the third decade, 8 in fourth, 5 in second, and 2 each in fifth and sixth, and one in seventh decade of life. In 25, the disease was in the right base and in 10 in the left base. In 2, both bases were involved. In all, the sputum was positive for tubercle bacilli. Every patient showed roentgenological evidence of parenchymal infiltration and in all but 2 cavitation was present. The lesions appeared exudative in all. There was nothing to suggest either calcification or fibrosis at the time of admission.

Pneumothorax alone was given in 15 cases. Pneumothorax with phrenic nerve operation was done in 8 cases. Pneumothorax plus pneumoperitoneum was administered in 2 cases. The remaining 12 were treated by bed-rest only.

In those receiving pneumothorax treatment, pleural effusion developed at some time during the course. In 2 patients the fluid was haemorrhagic and in 3 tubercle bacilli were found in the sediments.

Of these 37 cases, 20 (54 per cent) are apparently cured and have been working for five years or more without symptoms. Eight (21 per cent) are still ill and 9 (24 per cent) died.

The status of these 37 cases is compared with the ultimate results of 131 patients with upper lobe tuberculosis treated in the same hospital during the same period. In the latter series, 56 (42 per cent) are now in good health, 29 (22 per cent) are unimproved and 46 (35 per cent) died (1).

DISCUSSION

Comparison of these two groups indicates that the prognosis in basal pulmonary tuberculosis parallels that of upper lobe tuberculosis. Further analysis of the series indicates that those cases who are now working and in good clinical condition are patients in whom the cavities were made to collapse early by artificial pneumothorax with or without phrenic nerve paralysis.

Tuberculous lesions located in the lower parts of the lungs are influenced by the movement of the diaphragm. In the lateral view of the chest the normal

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diaphragm slopes rather sharply downward from anterior to posterior. Anteriorly the costophrenic angle is shallow and almost a right angle, while posteriorly it is deep and acute. Thus the anterior portion of the diaphragm is relatively fixed as compared with the central and posterior portions. On deep inspiration, therefore, the central portion descends almost vertically while the posterior and lateral portions move obliquely inward and downward. The acutely angled posterolateral extremities of the lower lobe descend deeply into the costophrenic angle. In normal subjects the motion of the posterior and central portions of the lower lobe appears to be from two to four times as great as that of the anterior portion. Actual measurement of diaphragmatic excursion in normal adults showed that the anterior portion descends from zero to one and one-half inches, the posterior portion from two and one-half to four inches on deep inspiration.

When the diaphragm is elevated by means of an abdominal support or phrenic nerve paralysis, it ascends into an exaggerated expiratory position. The central portion of the diaphragm is elevated straight upward; therefore basal cavities located centrally seem better collapsed. The posterior portion of the lower lobe is compressed in an obliquely upward and outward direction, this providing almost as much collapse of posterior lesions as central ones by reason of the increase in depth of the costophrenic angles.

The cavities not readily collapsed by pneumothorax were those located near the hilum; some of them grew larger under collapse. At autopsy such cases showed tuberculous bronchial stumps acting as a one-way valve. It appears that during inspiration, with general widening of the bronchial lumen, air enters such a cavity through the stump, but during expiration, with general narrowing of the bronchi, the ulcerocaseous lumen of the stump becomes completely closed, thus preventing egress of air and acting as a one-way valve. When a considerable amount of fluid collects within the cavity, such bronchial stumps may find themselves dipping into the fluid. During inspiration air may bubble through the fluid, but any egress of air during expiration may be impossible. Bronchoscopy in such cases may show nothing significant within the bronchi, although pathological examination of the ends of the bronchial stumps will most likely reveal extensive tuberculous changes. The apparent enlargement of the cavity in such instances as shown by roentgenograms may not be due to actual destruction of the pulmonary parenchyma but probably to distention of the cavity by air trapped within it. When the stump sloughs off, the cavity may be collapsed by applying pressure outside the lung by pneumothorax. At autopsy, some of the so-called hilum cavities seen in the postero-anterior films of the chest were located in the upper lobes near the sternum. They were unusually difficult to collapse during life.

In the treatment of basal tuberculosis, prevention of accumulation of secretions in the dependent portions of the bronchial tree is particularly important. When an accumulation of the secretion is permitted, there is a definite tendency on the part of the diseased portion of the lung to cavitate more readily. Adequate drainage of the lower lobes is not always possible with phrenic paralysis. In this respect the abdominal support has an advantage which phrenic nerve paralysis lacks.

In cases in which the drainage from the diseased areas in the lower lobes is inadequate, bronchoscopic drainage is useful, as shown repeatedly by Dr. Louis H. Clerf, of Jefferson Hospital (2).

The routine treatment of effusion complicating pneumothorax has been repeated aspirations, thereby rendering the pleural surface relatively dry. This prevented the pleura from being covered with layers of fibrin which would harbor the tubercle bacilli. Repeated aspirations resulted in a reduction in the formation of fluids, lowered bacillary count and decreased toxaemia.

It has been stated that frequent thoracocentesis causes sinus formation. On the contrary, infrequent aspiration which allows a steady rise of the intrapleural pressure due to the accumulation of the pleural fluid and tilting of the aspiration needle are the important contributing causes. The needle was introduced directly through the chest wall; tilting the needle would widen the tract and favor sinus formation. In chronic effusions with pleural fibrosis the peripheral portion of the diaphragm often became adherent to the chest wall with complete obliteration of the costophrenic sulcus. As the pleural fibrosis continued, the outer fringe of the diaphragm gradually was drawn upward. When this occurred a pocket was formed between the medial surface of the diaphragm and the lung in which the fluid collects. In removing the fluid an 18-gauge curved needle was useful since it might be directed easily into the pocket by riding over the peaked diaphragm. Following each aspiration, the patient lay on the opposite side for one or two hours, thereby permitting the needle tract to close. Whenever possible, aspiration of the fluid was done in the posterior axillary line since the patients seem to experience less pain when a needle is introduced in the posterior axillary area than in the anterior axillary region. With marked fibrinous exudate sterile physiological salt solution was useful to thin out the fluid, thereby facilitating aspiration. Antisepic solutions used in some cases seemed to coagulate the fibrinous exudate, especially in haemorrhagic fluids. In the patients with small residual pleural pockets, irrigation of them with physiological salt solution followed by the instillation of a sclerosing agent, quinine urea hydrochloride, 5 to 10 per cent, 1 to 10 cc. aided in developing fibrosis of the pleura and eventual closure of the space. This technique has also been effective in closing sinuses caused by aspiration. Pledgets soaked in quinine urea hydrochloride, 5 per cent solution, were introduced into the sinus every two days and allowed to remain about fifteen minutes. After a week or two, the sinus was usually closed (Savacool (3)).

Haemorrhagic effusions were also treated by repeated aspiration. When pyogenic organisms were discovered in the fluid, sulfadiazine was administered orally with apparently beneficial effects. The initial dose was 2 g., repeated in four hours; following the second dose, 1 g. was given every four hours for three days. It was noted in some cases that the sulfadiazine level in the pleural fluid was higher than that of the blood, the concentration in one case being 4.2 mg. for 100 cc. of blood, and 5.1 mg. for the same amount of the pleural fluid, indicating that the drug was retained in the pleural cavity.

Regarding the clinical features, the present study confirms our earlier observations (4, 5, 6).

The onset of basal pulmonary tuberculosis was usually insidious with occasional cough, slight expectoration, weakness and loss of weight. Haemoptysis and pleurisy were not uncommon. The sputum was rarely foul. As the disease progressed, there was usually an afternoon rise of temperature but it was rarely more than three-fifths of a degree. Even in patients with rapid spread of the lesions with cavitation, prostration and high fever were infrequent. Profuse expectoration occurred in the later stages often leading to the mistaken diagnosis of basal suppuration. The sputum was usually free from odor, unless there was an associated abscess or bronchiectasis. In some cases the onset was abrupt, resembling pneumonia, with severe pain in the chest radiating to the shoulder on the same side, elevation of temperature to 100 or 102°F., dyspnoea and night sweats. The physical signs were delayed expansion, increased vocal fremitus, impaired percussion note, exaggerated breath sounds and coarse râles. The signs varied, depending usually upon the presence or absence of retained secretions. The lesions were usually unilateral and the right side was more frequently affected. The disease appeared to be more common in women. Tubercle bacilli were found only after repeated examinations or following bronchoscopy. Associated involvement of other organs was rare. Roentgenologically, the cavitation resembled pulmonary abscess. The infiltration suggested bronchiectasis, unresolved pneumonia, new growth or mycotic infection. The walls of the cavities, as compared with those of pulmonary abscess, were usually thin, regular in outline and clear in detail. There was rarely a fluid level in the cavity, or, when present, the amount of fluid was small. The density of the surrounding lung field was less marked than in true pulmonary abscess or pneumonia. Associated atelectasis was rare. The important diagnostic features of basal pulmonary tuberculosis were the absence of striking toxic manifestations, such as marked weakness, loss of weight, high fever and night sweats. Repeated sputum examinations together with the examination of the gastric contents for tubercle bacilli were made. Bronchoscopy was of definite value in diagnosis and should be employed in doubtful cases.

SUMMARY

1. Between 1933 and 1943, 37 patients with basal pulmonary tuberculosis were treated. Thirty were female and 7 male. In 25 the disease was in the right base, in 10 in the left base and in 2 in both bases.

2. Twenty (54 per cent) of the series are apparently cured and have been working, 8 are still ill and 9 died. The percentage of apparent cure, morbidity and mortality of this series appears the same as those having apical tuberculosis.

3. Treatment with artificial pneumothorax with elevation of the diaphragm by phrenic nerve paralysis or abdominal support seems most satisfactory.

4. The cavities not amenable to collapse showed, at autopsy, bronchial stumps acting as one-way valves.

5. Pleural effusions, serous or haemorrhagic, were treated by repeated aspirations with good results. Sulfadiazine given orally appeared to lessen pyogenic infection of the fluid.

SUMARIO

1. De 1933 a 1943 se trató a 37 enfermos de tuberculosis en las bases de los pulmones: 30 mujeres y 7 varones. En 25 la enfermedad radicaba en la base del lado derecho, en 10 en la del izquierdo, y en 2 en ambas.

2. Veinte enfermos (54 por ciento) de la serie están aparentemente curados y han vuelto al trabajo, 8 están todavía enfermos y 9 han muerto. Los porcentajes de curaciones aparentes, morbidad y mortalidad en esta serie parecen ser idénticos que en los casos de tuberculosis de los vértices.

3. El neumotórax terapéutico, unido a la elevación del diafragma mediante la parálisis del frénico o el soporte del abdomen, parece ser el tratamiento más satisfactorio.

4. Las cavernas rebeldes al colapso mostraron en la autopsia muñones bronquiales que actuaban como válvulas de una vía.

5. Los derrames pleurales, serosos o hemorrágicos, fueron tratados con aspiraciones repetidas, siendo el resultado bueno. La sulfadiazina, administrada por vía bucal, al parecer atenuó la infección piógena del líquido.

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BOECK'S SARCOID AND SYSTEMIC SARCOIDOSIS [1, 2, 3]

(Besnier-Boeck-Schaumann Disease)

A Study of Thirty-five Cases

DAVID REISNER

Part I

Clinical Observations

(Section II) [4]

C. *Skin:* The presence of characteristic skin lesions is an important aid in the diagnosis of sarcoidosis. However, as pointed out before, cutaneous manifestations are not an essential part of the disease for they may be absent throughout the entire course in a large proportion of the cases. Among the 35 cases of this series, skin lesions were observed in 14 instances, or in 40 per cent.

The types of skin lesions described under a variety of names, such as miliary lupoid of Boeck, subcutaneous sarcoid of Darier-Roussy, Besnier's lupus pernio, apparently represent clinical variants of a basically identical condition. While these forms differ as regards the location and certain morphological features of the lesions, they all show essentially the same histological structure. Furthermore, since such skin manifestations are almost invariably associated with systemic involvement, it does not seem justified to regard them as separate entities. A number of dermatologists, such as Volk (48), Grschebin (12), Goeckerman (10) and others, have expressed a similar view.

As originally described by Boeck (3, 4, 5), the cutaneous sarcoid may be classified into three main forms, namely: the discrete nodular type, the large nodular and the diffuse infiltrating plaque-like varieties. Combinations between these forms are frequently encountered, lesions of more than one type occurring in the same patient (figure 8). Several cases of this series showed changes suggestive either of the Darier-Roussy form of subcutaneous sarcoid or subcutaneous lesions of the lupus pernio type. However, no sharp line of demarcation can be drawn between these various types, as two or more of those mentioned may be represented in the same patient, either simultaneously or successively at different periods during the course of observation.

The skin changes show a tendency to symmetrical distribution and are usually of a disseminated character, although in some cases they may be more localized. In order of frequency of involvement the following locations were found in this

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[2] A preliminary report on this material was presented at the annual meeting of the National Tuberculosis Association in Boston, June, 1939. An abstract of the report appears in the Transactions, 1939, page 107.

[3] The present paper deals with the clinical aspects of the disease. A report on the pathological findings, including biopsy and autopsy material, together with a discussion of the pathogenesis, will appear in a subsequent issue of the REVIEW.

[4] Section I of this paper appeared in the April, 1944 issue of the REVIEW.

group of cases: upper and lower extremities, usually their extensor surfaces; nose, particularly the alae nasi and the tip; the cheeks; neck; chest and abdomen;

FIG. 8. Photographs illustrating types of cutaneous lesions in three different patients. A: (Top) disseminated discrete nodules on the neck, around the eyelids and on the ear; larger plaque above the eyebrow. B: (Lower left) nodules arranged in groups on the thigh and leg, some of them in the stage of healing. C: (Lower right) irregularly shaped flat plaques of various sizes distributed over the back.

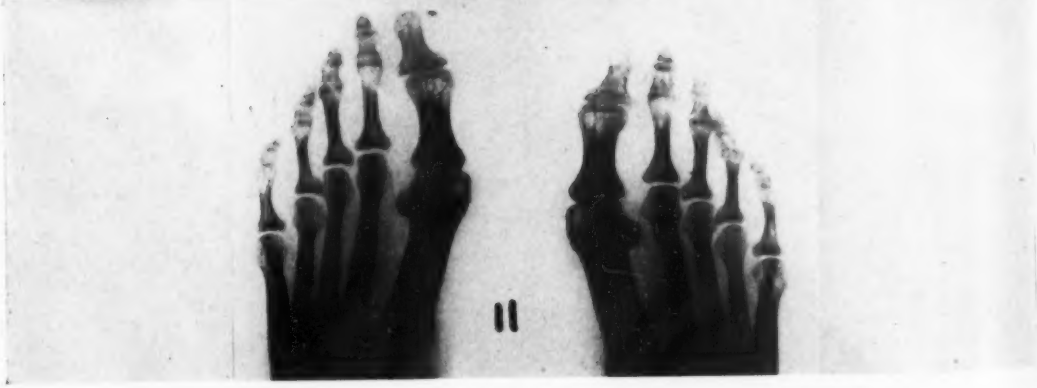
eyelids and ears. The subcutaneous nodules show a predilection to involve the fingers, less frequently the toes, about the interphalangeal articulations and are usually associated with osseous changes.

As in other localizations of sarcoidosis, spontaneous regression is apparently a frequent occurrence in skin lesions as well. In 7 cases, or in one-half of those showing cutaneous changes, definite healing could be observed. In the remainder the lesions were either stationary or presented regression in some places alternating with development of new eruptions in others. Healing may be either complete without leaving any residue or an atrophic scar may form in the course of involution. The lesions as a rule do not ulcerate, occasionally scaling may occur in the course of healing.

In 2 cases of this series skin lesions showing clinical features and histological findings consistent with a diagnosis of lupus vulgaris were present simultaneously with characteristic sarcoid lesions. Similar observations, suggesting transition of cutaneous sarcoid into lupus vulgaris or ordinary skin tuberculosis, have been reported by Goldschmidt (11), Propper (33) and others. Such occurrences may represent an analogy with transformation of the pulmonary changes associated with sarcoidosis into active and progressive tuberculosis, as referred to in an earlier paragraph.

In recent years a number of dermatologists have called attention to certain peculiarities of cutaneous tuberculosis in the American Negro, a point which merits some consideration here, particularly since the material of this study consisted largely of Negroes and also because in some of the cases the skin lesions were considered as somewhat atypical for sarcoid. Klauder (21), Crawford (7), Nomland (30) and Bloom and Mendelsohn (2) in reporting such cases variously refer to them as "sarcoid-like granulomas," "cutaneous tuberculosis of the anergic type" or "haematogenous cutaneous tuberculosis." Thomas (46) speaks of a "sarcoid type of tuberculosis." The skin manifestations observed in those cases apparently did not fit into any of the established classifications and it seems that they may occupy a borderline position between typical sarcoid and ordinary tuberculosis. The tuberculin reaction was found to be positive in most of these patients and some of them subsequently developed manifest caseous tuberculosis in various organs. However, in reviewing the cases included in those reports, it appears that the majority of them showed indications of more or less wide-spread systemic involvement and the histological findings on biopsy were essentially those observed in sarcoidosis. It would seem that such atypical cases, perhaps just because they present departures from the "classical" pattern showing various gradations of transition from sarcoid to ordinary tuberculosis, may be of particular significance for the understanding of the pathogenesis of the disease.

D. *Bones:* Skeletal involvement in its characteristic form may be regarded as practically pathognomonic for sarcoidosis and therefore of great diagnostic value. In this material, radiographic evidence of bone changes was found in 9 cases, or in about one-fourth of the group. In view of the disseminated character of the disease, it is very probable that anatomical involvement of the skeletal system is more frequent than indicated by the roentgenological findings. As pointed out by Schaumann (40), both the roentgenogram and the macroscopical



FIGS. 9–11

specimen may present an entirely normal appearance in the presence of granulomatous infiltration limited to the bone marrow.

The typical radiographic appearance of the osseous changes, particularly the picture of the so-called *osteitis tuberculosa multiplex cystoides* of Jüngling (18, 19), has received sufficient attention in the literature and therefore need not be described here in detail. It should be noted, however, that the cyst-like changes usually found in the phalanges of the fingers and toes, though quite characteristic, represent only one of several forms of bone involvement encountered in sarcoidosis.

A distinction must be made between the following main types: (*1*) The circumscribed form, consisting of sharply defined "punched-out" areas of rarefaction, either circular or oval in shape, usually situated in the medullary portion, without any accompanying reactive changes. (*2*) The diffuse form, which produces either a lattice-like appearance of the bony structure due to multiple small irregularly shaped areas of rarefaction, or a diffuse finely reticulated lace-like pattern, or else a combination of both (figures 10 and 11). In the latter type the involvement usually extends over large portions of the bone, often causing alteration in size and shape with broadening of the shaft and thinning-out of the cortex. In occasional cases extensive changes of this character may result in destruction of the bone with marked mutilation, a type that may show some similarity with bone lesions observed in leprosy (figure 14). It should be emphasized, however, that, as in other localizations of sarcoidosis, there is no sharp line of demarcation between the individual types of bone involvement. Not infrequently transitions from one form into another take place in the course of observation and, furthermore, in many cases one finds the simultaneous presence of more than one type, either in different bones or even in adjoining areas of the same bone.

Although the osseous changes are most commonly found in the bones of the hands and feet, particularly in the phalanges and less frequently in the metacarpals or metatarsals, other parts of the skeletal system may be involved as well. In 2 patients of the present series the carpal bones and, in one, the ulna showed characteristic lesions. There was also one rather unique instance of generalized skeletal involvement with wide-spread changes in the bones of the upper and lower extremities including the hands and feet. A detailed report of this case will be found below.

Subjective symptoms due to the osseous changes are usually absent, but in the early stages slight pain may be present. Since the process, as a rule, does not

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FIG. 9. (Top) Fusiform swelling of fingers in the middle phalanges with trophic changes of the nails.

FIG. 10. (Same case as figure 9.) Roentgenograms illustrating characteristic bone lesions, predominantly located in the phalanges of the fingers of both hands. A: (Middle left) shows multiple circumscribed cyst-like areas of rarefaction as well as reticulation of a more diffuse character. B: (Middle right) (two years later) demonstrates considerable regression of the osseous changes.

FIG. 11. (Bottom) (Same case as figures 9 and 10.) Roentgenogram showing similar character of bone involvement in the phalanges of the toes.

extend into the articulation there is no limitation of function. In the majority of cases, there is, however, some external evidence indicative of bone involvement, usually in the form of fusiform nontender swelling of the fingers, less frequently of the toes (figure 9). In a number of instances the previously mentioned periarticular subcutaneous soft nodules may be found and occasionally dystrophic changes of the nails are present. The most pronounced degree of external deformity, usually of the fingers and toes, is observed in cases with extensive bone involvement of the mutilating variety (figure 13). In the present group all but one of the cases with radiographically demonstrable bone lesions exhibited some external manifestations at the site of involvement.

It may be of interest to point out that all except one of the cases in which bone lesions were present also showed skin manifestations, not only locally in proximity to the area of bone involvement, but often rather widely disseminated through the body. It would thus seem that bone changes are much more likely to be present in cases with cutaneous involvement than in the absence of the latter.

Spontaneous regression of the bone lesions is apparently not an infrequent occurrence. Two out of 6 patients who have had adequate follow-up observation showed definite indications of healing. Regression is more apt to take place in the diffuse type of involvement than in the circumscribed form. One may think in this connection of an analogy with the types of pulmonary involvement, that is, the diffusely disseminated form with its pronounced tendency to regression, as contrasted with the late manifestations of an irreversible character. The diffuse type of bone involvement may be looked upon as the result of an early dissemination with its potentialities of healing by apparent resolution. The localized cyst-like changes, on the other hand, generally represent a more stabilized phase of the disease in which healing may occur by organization and fibrosis, the latter constituting a permanent anatomical alteration.

The following case, whose total observation covers a period of fifteen years, is reported in some detail.

Case 31: M. J., a colored girl, nine years of age, was admitted to the Children's Hospital of Philadelphia in April, 1924, because of swelling of the upper lids of both eyes and swelling in the regions of both parotid glands of six months' duration. This was not associated with pain or any other discomfort. Her general health had been good.

Examination showed bilateral symmetrical nontender enlargement of the parotid and the lachrymal glands (figure 12). There was also some enlargement of the submaxillary salivary glands and several palpable lymph nodes were present in the axillary and inguinal regions. There were no other noteworthy findings on physical examination and the usual laboratory data did not reveal anything of significance. Roentgenogram of the chest was normal. An intracutaneous tuberculin test gave a negative result. Biopsy of the left lachrymal gland showed epithelioid and giant cell tubercles without necrosis. Acid-fast bacilli could not be found in the sections and guinea pig inoculation was negative for tuberculosis. She was discharged from the hospital after four months with the diagnosis of Mikulicz's disease.

Eight years later, in June, 1932, she was admitted to St. Luke's Hospital in New York City complaining of nasal obstruction of four months' duration, which she attributed to a preceding trauma. At about the same time she had noticed swelling of the fingers and toes apparently not associated with pain.

On examination a papillomatous area was found at the right ala nasi extending into the mucosa and causing narrowing of the orifice. There was infiltration of the mucous membrane of the larynx and epiglottis. The lachrymal glands and the parotid glands were not enlarged. There were enlarged lymph nodes in the cervical, submental, axillary, epitrochlear and inguinal regions. Firm nontender masses were felt in both breasts. The spleen was palpable about two fingers below the costal margin. The fingers and toes showed considerable deformity with shortening and fusiform swelling, but no tenderness. Roentgenogram of the chest showed nodular and strand-like infiltration in the upper lung fields, more pronounced on the right side. Roentgenograms of the hands demonstrated marked changes of the bony structure of all the phalanges and metacarpals

FIG. 12. (Case 31) Photograph of patient in 1924, at the age of nine, showing enlargement of the lachrymal gland bilaterally and marked swelling of both the right and left parotid gland. Clinical picture of Mikulicz's syndrome.

with diffuse lace-like rarefaction and multiple round, oval and irregularly shaped "punched-out" areas. Some of the phalanges showed deformity with broadening and shortening, as well as destruction with breaking up into fragments (figure 14A). Similar changes were noted in the phalanges of the toes. The distal portions of the bones of the right and left forearm, as well as the right and left tibia and the right fibula, showed large areas of rarefaction (figures 15A and 16A). There were no significant laboratory findings. Biopsy of an epitrochlear lymph node showed numerous tubercles composed of epithelioid and giant cells with some hyalinized fibrosis in the periphery but no caseation. The patient was discharged from the hospital after two months without apparent change in her condition or objective findings.

Seven years later, in January, 1939, she came under observation at one of the chest

FIGS. 13–14

clinics of the Department of Health following routine chest X-ray examination in the course of a mass survey. A short time after her discharge from the hospital in 1932 she had developed a skin eruption on the neck which had apparently healed leaving slight pigmented scars. The deformities of her fingers and toes had apparently increased in extent, but during the past five years had remained unchanged and caused no subjective symptoms. Her general health had been good since the last observation.

Examination showed discrete and conglomerate nodules around the alae nasi and on the cheeks. Over the right elbow there was a larger firm granulomatous patch with verrucous vegetations on the surface which presented the clinical picture of either lupus vulgaris or *tuberculosis verrucosa cutis*. There were no palpable superficial lymph nodes, the spleen could not be felt and the remainder of the physical examination, except for the deformities of the fingers and toes, was essentially negative. The fingers of both hands showed quite striking changes with marked shortening and irregular spindle-shaped enlargement. There was no pain or tenderness. The joints could be hyperextended and some of them presented evidence of subluxation (figure 13). Similar changes, less marked in degree, were present in the toes. Intracutaneous tuberculin tests gave a weakly positive reaction (one-plus) to 0.1 mg. of OT. The laboratory data were essentially irrelevant. Roentgenogram of the chest showed minimal stringy fibrosis in the apical areas of both lungs. Roentgenograms of the hands demonstrated extensive destruction of the bones with mutilating deformities, particularly marked in the distal and middle phalanges. Multiple sharply circumscribed areas of rarefaction were present in the phalanges and metacarpals. Alongside with these changes there was evidence of considerable repair in the appearance of the bony structure, notably in the metacarpals and in some of the proximal phalanges, as compared with the findings observed in 1932 (figure 14B). Similar changes were present in the bones of the feet. The bones of the forearms and legs showed almost complete regression of the changes demonstrated seven years previously. Residual areas of rarefaction were still present in the distal ends of the radius and ulna on both sides (figures 15B and 16B).

Biopsy from the cutaneous lesion around the ala nasi showed numerous tubercles in the deeper corium composed of epithelioid and giant cells of the Langhans type with a peripheral zone of fibroblasts but no necrosis. Acid-fast bacilli could not be found in the sections and inoculation of the tissue into guinea pigs did not produce tuberculosis. Biopsy from the skin lesion located in the region of the elbow showed tubercle structure, consisting of epithelioid and giant cells with central areas of caseation. Acid-fast bacilli were not seen in the sections. The tissue was inoculated into a guinea pig. The animal died after eleven days from an intercurrent infection, autopsy showing enlarged lymph nodes without evidence of tuberculosis. This material was again inoculated and autopsy

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FIG. 13. (Top) (Case 31) Photograph of hands in 1939, showing extensive deformities of all fingers with marked shortening and fusiform swelling.

FIG. 14. (Case 31) Roentgenogram of June, 1932 (A) (Middle) shows diffuse lace-like rarefaction of the bones of both hands with circumscribed "punched-out" areas in the phalanges and metacarpal bones. Note deformities of some of the bones with broadening and shortening, and destruction with division into fragments in one of the terminal phalanges. In January, 1939 (B) (Bottom) there were extensive mutilating deformities of the phalanges with multiple circumscribed areas of rarefaction. At the same time the general appearance of the bony architecture indicates marked regression of the diffuse involvement previously noted.

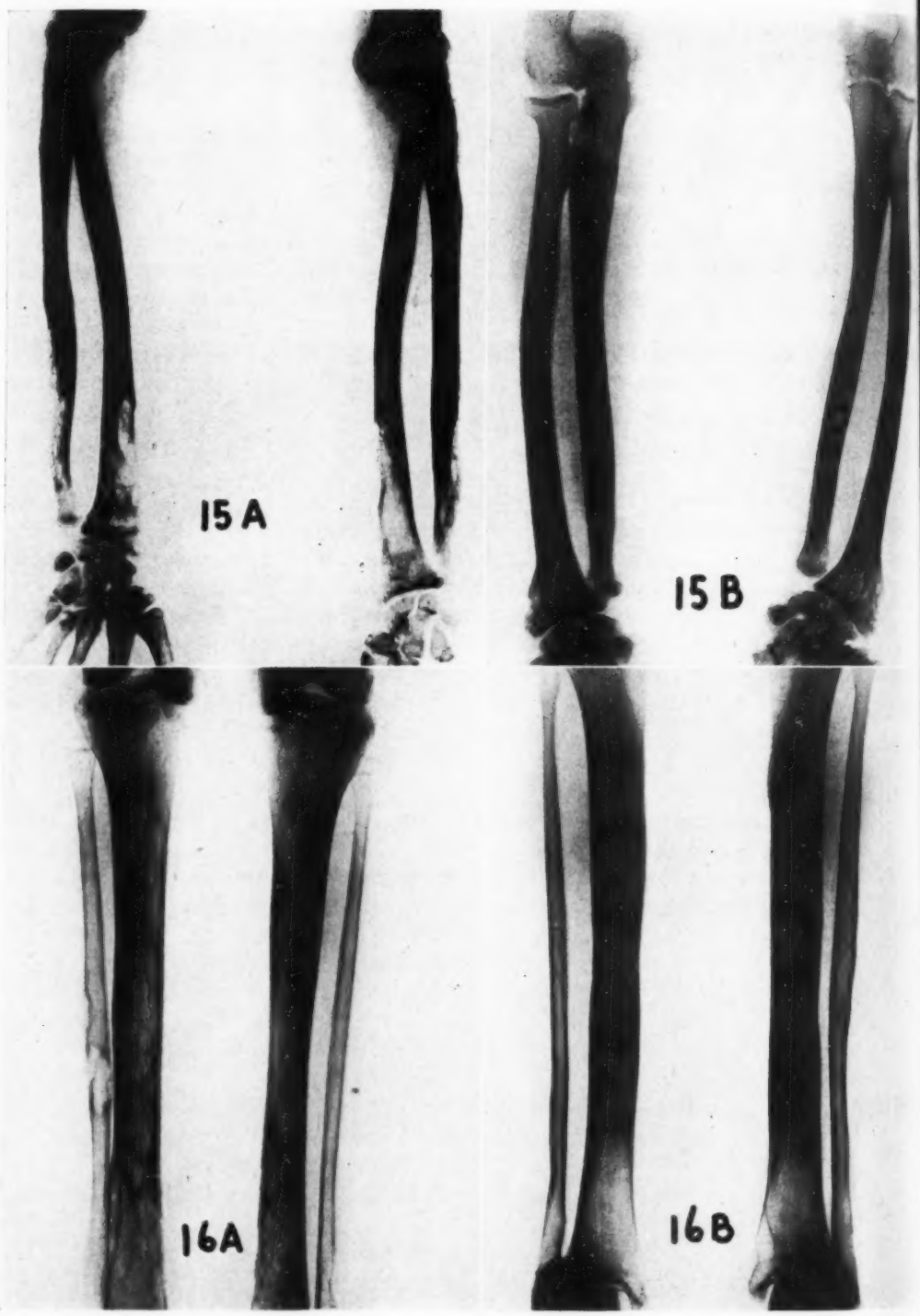

FIG. 15. (Case 31) Roentgenogram of both forearms of June, 1932 (A) (Upper left) shows diffuse rarefaction in the distal thirds of both the right and left radius and ulna. In January, 1939 (B) (Upper right) there was marked regression of the changes. Residual rarefaction may be noted in the distal ends of the bones.

FIG. 16. (Case 31) Roentgenogram of 1932 (A) (Lower left) shows diffuse involvement of the bones of the legs with practically complete regression in 1939 (B) (Lower right).

of the animal two months later showed caseous tuberculosis of the inguinal lymph nodes. Acid-fast bacilli were found in the sections

The patient has not been heard from since December, 1939.[5]

Comment: This case illustrates the variability of the clinical picture of sarcoidosis and demonstrates the evolution of the process through several distinct phases. The initial manifestations were those of Mikulicz's syndrome. This was followed a number of years later by the development of a wide-spread generalized disease with involvement of the skin, mucous membranes, lymph nodes, bones, lungs and spleen. Subsequently there occurred marked regression of the organic manifestations leaving residual changes of an apparently permanent nature. A remarkable feature was the presence of extensive bone involvement of a systemic character which resulted in marked deformity with mutilation. Another noteworthy finding was the coexistence of ordinary tuberculosis of the skin and typical sarcoid lesions.

E. *Spleen and liver:* Involvement of the spleen and liver represents a comparatively frequent finding in sarcoidosis. Pathological observations would indicate that participation of these organs in the systemic process is probably more common than can be detected clinically. In a group of 6 cases observed at necropsy, Nickerson (29) found lesions in the spleen in 5 instances, in 4 of which definite splenomegaly was present.

In the material of this study there was clinical evidence of splenic enlargement in 8 cases. In one of these, however, the extensive involvement of the spleen subsequently proved to be due to caseous tuberculosis as part of a terminal generalized haematogenous dissemination. Usually the enlargement of the spleen is within moderate limits, although occasionally it may be quite marked and the most impressive feature in the clinical picture, as found in one patient of this series. In this case the spleen filled practically the entire left side of the abdomen and extended to the level of the crest of the ilium. Splenectomy was subsequently performed, the removed specimen weighing 1,030 g. Similar instances have been observed by Askanazy (1), Gebsattel (9), Secretan (41) and Klemperer (22). Cases of this type may suggest a clinical diagnosis of Banti's syndrome, as indicated by some of the reports mentioned.

Involvement of the liver is apparently both less conspicuous and less frequent than splenic involvement. Enlargement of the liver of a slight to moderate degree was found in 6 cases. In 3 additional patients in whom hepatomegaly appeared in the course of observation the enlargement of the organ could not be considered a part of the original disease process. In 2 of these cases congestive

[5] The author is indebted to the late Dr. J. Crozer Griffith of Philadelphia, and to Lea & Febiger, Publishers of the American Journal of the Medical Sciences, for their permission to include the early part of the case report and a photograph of the patient from Doctor Griffith's article *Mikulicz's Disease and Mikulicz's Syndrome*, Am. J. M. Sc., 1929, *178*, 853. Appreciation is also expressed to the Medical Director of the St. Luke's Hospital, New York City, and to Dr. Leila C. Knox, Pathologist of that institution, for permission to review the hospital records and the loan of roentgenograms and biopsy material.

heart failure was apparently the cause of the hepatic enlargement and the third case was the previously mentioned patient who died as a result of generalized haematogenous tuberculosis with involvement of both the spleen and liver.

Splenic and hepatic enlargement is apparently more apt to be found in the early phase of the disease as part of active dissemination. During the later stages the size of these organs may regress to a point where they cannot be palpated. In several cases definite regression was noted under observation, generally within a period of several months, simultaneously with a similar behavior of the lesions in other parts of the body. In some cases, however, the enlargement of the spleen or liver may persist throughout an extended follow-up period.

F. *Heart:* The heart may become involved in two ways, either through direct invasion by sarcoid tissue, particularly of the myocardium; or indirectly, as a result of extensive pulmonary changes of long standing which may eventually cause right heart failure.

The significance of heart involvement in sarcoidosis was recently emphasized by Longcope (26) who observed 5 cases with clinical and electrocardiographic evidence of heart disease which eventually resulted in failure. Two of those cases showed extensive involvement of the myocardium at autopsy. Similar findings have been previously reported by Salvesen (36), Garland and Thompson (8), Souter (43) and Schaumann (39). Cotter (6) described a case of an eighteen year old Negro who had died from cardiac failure apparently caused by extensive infiltration of the heart muscle with lesions characteristic of sarcoid.

In our own series 2 cases showed clinical and electrocardiographic findings indicative of cardiac involvement. Of these, one patient presented definite signs of congestive failure from which he subsequently apparently recovered, but was later lost from observation. Another patient who terminally presented symptoms and signs of heart failure had extensive pulmonary changes of long duration. Since permission for autopsy was not obtained in this case the question must remain open whether the cardiac failure was the result of the chronic lung condition or due to actual invasion of the heart by sarcoid.

Two other cases presented some abnormalities in the electrocardiogram in the absence of clinical signs or symptoms indicative of heart disease. Both of these patients have been followed for several years and up to now have shown no clinical evidence of cardiac disturbance.

G. *Eyes:* The eyes or their adnexa are found to be implicated in a considerable proportion of the cases of sarcoidosis. Among the recently reported series of Longcope (26), Snapper and Pompen (42) and Harrell (14) eye involvement was observed in approximately one-half of the cases. In the present group ocular manifestations, including involvement of the lachrymal glands, were found in 9 cases, or in about one-fourth of the total. Such discrepancies, however, may well be due to variations in the sources of selection of the material included in the various reports.

It seems that practically every part of the eye or its adjacent structures may

become involved in the course of the disease. Levitt (24) has recently published a comprehensive review of the various observations dealing with the ocular manifestations which would indicate that the most frequently involved structure is the uveal tract, usually in the form of iridocyclitis. It is now generally recognized that the syndrome of "uveo-parotid fever" of Heerfordt (16) is a part of the systemic disease, since it is almost always associated with wide-spread visceral manifestations. Nor are the lesions of the uveal tract necessarily connected with parotid involvement. Ocular manifestations may exist without parotid enlargement and, conversely, involvement of the parotid gland may be found in the absence of any eye affection.

Among the 9 cases presenting ocular manifestations, iridocyclitis was found in 5, 2 cases showed only corneal and conjunctival changes and in 2 instances enlargement of the lachrymal glands was present without changes in the eye proper. The involvement is generally bilateral, although in occasional cases the lesion may be limited to one side.

The fate of the lesions affecting the eye, especially those of the uveal tract, is apparently quite variable. While a number of cases with iridocyclitis show complete, apparently spontaneous, healing with restitution to normal, in a good many others permanent damage may cause marked functional impairment, not infrequently resulting in blindness. Three cases included in this series developed extensive and progressive eye involvement eventually resulting in phthisis bulbi, with total blindness in 2 and blindness of one eye in one patient. In 2 of these cases enucleation was performed. That the ocular lesions, particularly those involving the uvea, may often lead to rather serious consequences is indicated by similar observations recorded by Tanner and McCurry (45), Ramel (34), Longcope (26) and others. The cases in which the lesion appeared to be limited to the conjunctiva and cornea, as well as those with involvement of the lachrymal glands, showed complete regression during the follow-up observation.

H. *Parotid gland:* Involvement of the parotid gland was found in 4 cases, in 2 of which it was associated with eye changes. In the remaining 2 there was no eye involvement present, indicating that the parotid gland may participate in the disease process independently of eye manifestations.

One case, in which the parotid enlargement was associated with involvement of both the lachrymal and submaxillary salivary glands presented the clinical picture of Mikulicz's syndrome, a combination occasionally observed in cases of sarcoidosis (figure 12). There is apparently no specific aetiology for the disease or syndrome described by Mikulicz and it would seem that sarcoidosis may account for at least some of the cases in which a combination of such findings occurs, generally as part of a more wide-spread systemic affection.

The involvement of the parotid and other salivary glands is usually bilateral and symmetrical. The swelling is, as a rule, of moderate size, painless and nontender. In some cases it may be associated with enlargement of the pre- and postauricular lymph nodes, but the latter may also be found without parotid enlargement. In such instances one must be careful not to mistake lymph-

adenopathy in that region for parotid involvement. Spontaneous regression of the changes involving the parotid and the other salivary glands is apparently a frequent occurrence, usually in conformity with a similar behavior of the lesions in other parts of the body.

I. *Mucous membranes:* In 4 cases the mucous membranes of the respiratory passages were found to be involved. In 2 of these, the lesion appeared to be limited to the nasal mucosa, biopsy confirmation having been obtained in one. In the other 2 patients there was extensive infiltration of the pharynx, the epiglottis and larynx. While in some cases cutaneous lesions about the nostrils may extend directly into the mucosa, there are others in which the involvement of the mucous membranes, either in the nose or elsewhere, is apparently an independent manifestation of the disease. It is interesting to note that Boeck (4) in one of his early publications called attention to the involvement of the mucous membranes in sarcoid. Since then, lesions of the mucous membranes in various parts of the body, but especially in the respiratory tract, have been found by other observers. It is possible that thorough routine investigation in this direction in all cases suggestive of sarcoidosis would reveal more frequent clinical evidence of such involvement.

None of the cases of this series showed any significant symptoms or serious consequences resulting from the lesions of the mucous membranes. Spontaneous regression occurred in all 4 instances. However, judging from the extent of involvement observed in some cases, it is quite conceivable that occasionally permanent structural damage with functional impairment may result from such changes.

J. *Other localizations:* In view of the wide-spread disseminated character of sarcoidosis, anatomical involvement of various other organs would be expected to occur more often than clinical evidence indicates. At necropsy Nickerson (29), Spencer and Warren (44) and others observed lesions in a variety of organs, such as the thyroid gland, pancreas, kidneys, adrenals, the mucosa of the trachea and bronchi, epididymis, testis and peripheral muscle. Such involvement may cause no clinical manifestations unless the changes are of sufficient extent and of suitable location to permit their clinical recognition.

Among the cases of this series there was one patient who presented findings pointing to a lesion in the sacral segment of the spinal cord. Complete disappearance of the neurological signs and symptoms occurred in the course of observation. Paralysis of the facial nerve was observed in a patient with enlargement of the parotid gland. With regression of the parotid involvement the signs of facial palsy disappeared. As pointed out by Heerfordt (16), paralysis of the facial nerve occurs in some cases presenting the uveo-parotid syndrome. The paralysis is apparently of the peripheral type, secondary to the parotid enlargement, and is usually of a transient character.

Attention has been called to the occurrence of *diabetes insipidus* in occasional cases of sarcoidosis. Tillgren (47) and Longcope (26) had the opportunity to

observe such cases in which autopsy disclosed extensive infiltration of the pituitary gland by sarcoid tissue. One of our patients presented clinical findings suggestive of *diabetes insipidus*. No pathological confirmation of actual pituitary involvement could be obtained.

Lesions in the breasts, consisting of firm, nontender and freely movable masses, were noted in 2 cases in both of whom the changes appeared to have regressed during the follow-up period.

Two patients showed involvement of the serous membranes. One of these, in the course of observation, developed peritoneal effusion associated with effusion in the right pleural cavity. Complete absorption of both occurred within a period of several months simultaneously with marked regression of the other visceral manifestations. While it is not certain that the polyserositis actually represented a part of the systemic disease, it should be pointed out that there were no clinical or laboratory findings to suggest any other causative factor to account for such involvement. A second patient, who had been under observation for sarcoidosis for a number of years, developed pleural effusion from which she recovered within a period of a few months. Five years later, however, she succumbed to rapidly progressive and destructive pulmonary tuberculosis. It is possible that in this case the pleural effusion was the precursor of the active tuberculous process which became manifest years later.

Involvement of the tonsils has been particularly emphasized by Schaumann (38) who found invasion of the tonsillar tissue by sarcoid in the majority of his cases. Since the tonsils are part of the lymphatic system, this observation would be in keeping with the particular predilection of this disease for the lymphatic structures. Although usually there are no conspicuous clinical findings on the part of the tonsils, this does not preclude the presence of microscopical involvement. In 2 cases of this series the tonsils were examined histologically and changes characteristic of sarcoid were observed in one. In some cases biopsy from the tonsil may be of value for confirmation of the clinical diagnosis, especially in the absence of other material, such as superficial lymph nodes or skin lesions.

TUBERCULIN REACTION

The tuberculin reaction occupies a place of considerable significance in the discussions on sarcoidosis. From a clinical point of view the diagnostic value of a negative tuberculin test has been stressed by a number of observers. The reactivity to tuberculin has also been widely debated in connection with the controversy regarding the relationship between sarcoidosis and tuberculosis. The presence of tuberculin anergy, observed in the majority of cases of sarcoidosis, has been used as an argument both for and against the tuberculous aetiology. A more detailed discussion of the question of tuberculin sensitivity and its possible pathogenetic significance will be taken up in a subsequent part of this report.

All cases included in this series have been tested by means of the intracutaneous Mantoux method and Old Tuberculin was used throughout. In the majority of the cases repeated testing was performed with graded dilutions of tuberculin,

usually starting with a dilution of 1:100,000, or 0.001 mg. If no definite reaction was noted the dose was progressively increased up to 1.0 mg., in a number of cases up to 10.0 mg. Table 3 shows the results observed in the group of 35 cases, indicating the total number of persons tested with each strength and the numbers of positive and negative reactions obtained.

Of the entire group, 14 cases, or 40 per cent, reacted positively, while 21 patients, or 60 per cent, showed no reactions up to 1.0 mg. Ten patients were tested with 10 mg., all showing negative results. In those cases that reacted positively the skin reactions were for the most part weak, only in very few instances were they of a moderate or marked degree. None of the cases showed focal or constitutional reactions.

The proportion of reactors found in this series coincides with the figure of 40 per cent observed by Kissmeyer (20) and approximates the figure of 30 per cent as reported by Martenstein (27) on the basis of material compiled from various sources. It is worth noting, however, that a proportion of 40 per cent tuberculin reactors, as found in our group, appears to fall below the expected figure for a

TABLE 3

Results of tuberculin tests in 35 cases of sarcoidosis

TUBERCULIN STRENGTH	TOTAL NUMBER OF CASES TESTED	NUMBER WITH POSITIVE REACTIONS	NUMBER WITH NEGATIVE REACTIONS
mg.			
0.001	25	1	24
0.01	33	4	29
0.1	29	7	22
1.0	23	2	21
10.0	10	0	10

comparable average population. This is particularly true for a group such as this one which is composed of adult persons, largely Negroes, originating from congested urban areas. Even though for purposes of comparison with an average population the material is numerically small, these findings would seem to be of some significance.

A change in the tuberculin reaction, either reversal from negative to positive or an increase in the degree of sensitivity, was noted in several of the cases which developed frank tuberculosis under observation. In some of these patients the altered reactivity to tuberculin was found to have preceded the appearance of clinical manifestations of active tuberculosis for a period of several months to years. This would suggest that an increased sensitivity to tuberculin developing in a case of sarcoidosis may be more than a fortuitous occurrence and that it might signify potential transformation into manifest tuberculosis.

No systematic attempt was made to demonstrate in the blood serum the presence of "anticutins" which, according to Martenstein (27, 28), are assumed to be capable of either neutralizing or depressing the reactivity of the skin to tuberculin and which are apparently found in some cases of sarcoidosis. Through the courtesy of Dr. Max Pinner an effort was made in that direction in several of our patients, but the results were not conclusive.

LABORATORY FINDINGS

As regards the blood picture, the noteworthy deviations from the norm were as follows: increase in the proportion of the monocytes in about one-half of the cases and an increase of the eosinophils in approximately one-fourth of the group. The range of the increase in the monocytes varied between 8 and 20 per cent, that of the eosinophils between 6 and 14 per cent. Total white blood cell counts below the range of normal, usually due to a reduction in the number of neutrophils, were observed in about one-third of the cases. Changes in the blood picture, particularly increase in the monocytes, are more likely to occur in the early stages of the disease and during the phase of dissemination than in the chronic stationary forms. However, such findings were not sufficiently constant to indicate a definite correlation with either the stage or dynamic behavior of the disease.

The erythrocyte sedimentation rate was found to be increased in the majority of the cases of this series. This was observed not only in patients in whom the clinical findings indicated actual propagation of the disease, but also in a number of cases showing well stabilized chronic lesions without clinical evidence of activity over an extended follow-up period. There is as yet no satisfactory explanation which could account for such discrepancies between the clinical picture and the sedimentation rate. It seems doubtful, however, whether this test can be regarded as a reliable index of the stage of activity in sarcoidosis.

The occurrence of hyperproteinaemia and hyperglobulinaemia in sarcoidosis has been stressed by a number of authors, particularly by Salvesen (36), Waldenström (50) and Harrell and Fisher (15). Of 22 cases of this series in which serum protein determinations were performed, 8 showed total protein contents above 7.0 g. per cent and 6 of these the values were above 7.5 g. per cent. As noted by other observers, the hyperproteinaemia is usually due to an increase in the globulin fraction. Tendency to reversal of the albumin-globulin ratio was present in several patients in whom the total protein contents were within normal limits. It should be pointed out, however, that no apparent relationship could be observed between the clinical character of the disease and the presence or absence of hyperglobulinaemia. The significance of increased globulin contents in the serum in cases of sarcoidosis is not clear, particularly in view of the fact that similar findings are observed in a variety of other conditions.

Determination of the calcium and phosphorus levels in the blood did not reveal any findings which could be regarded as of significance in connection with the clinical manifestations or evolution of the disease. Phosphatase studies were not carried out in a large enough number of cases to warrant a definite statement as to the results obtained.

The blood Wassermann reaction was negative in 23 cases, positive in 10 and in 2 instances it was doubtful. All of the positive and doubtful reactions occurred among the 30 Negro patients of this series. No aetiological significance as regards sarcoidosis can be attached to this finding in view of recent observations (Vonderlehr and Usilton (49), Rosenthal (35)) indicating prevalence rates of 25 and 30 per cent positive serological reactions for syphilis among large

groups of the Negro population. In none of our patients was there any evidence that antiluetic therapy had influenced either the clinical manifestations or course of the disease. It may be of interest to point out that in some cases the positive serological reaction persisted despite intensive and prolonged specific treatment and that the reactions were sometimes inconstant, alternating between positive and negative. The possibility of nonspecific Wassermann reactions occurring in some cases of sarcoidosis, as suggested by Waldenström (50), may therefore deserve some consideration.

Examinations of the sputum and gastric contents for tubercle bacilli by means of the concentrated method, in a number of instances supplemented by cultures and guinea pig inoculations, were consistently negative throughout the period of follow-up, except in those patients who developed manifest pulmonary tuberculosis in the course of observation.

GENERAL COURSE AND PROGNOSIS

One of the outstanding general characteristics of sarcoidosis is the marked contrast between the extent of involvement in various organs and the apparently good general health of the patient. Constitutional signs and symptoms are absent in the majority of cases during the chronic stage and in patients presenting well stabilized lesions. However, the chronic stationary phase of the disease is sometimes preceded by a more acute or subacute period, usually of comparatively short duration. During that stage one may find constitutional symptoms and signs suggestive of a low-grade systemic infection, such as fatigue, loss of weight, joint pains and subfebrile temperature. It is very probable that this period corresponds with the phase of active dissemination of the disease. These symptoms usually subside after a period of several weeks to a few months as the case enters the chronic stage and the lesions in the various organs may either remain stationary or show marked regression. During this phase the patients, as a rule, remain free of constitutional symptoms despite extensive organic involvement. In some cases the development of new clinical manifestations may be accompanied by the appearance of a new train of symptoms of systemic nature. Symptoms or signs of a local nature due to the presence of lesions in some particular organ may or may not be present, depending on the extent and severity of such involvement. The development of manifest and progressive tuberculosis in the course of observation will usually result in a decided change in the general clinical picture.

In view of the extremely chronic duration and the unpredictable eventual outcome of the disease, an adequate period of observation is essential for the evaluation of its course as a whole. In analyzing the material from this point of view, 7 cases had to be eliminated from consideration because the follow-up period was deemed insufficient. The observations on the remaining 28 cases, with an average period of follow-up of five years, may be summarized as follows:

Regression of the lesions in various organs, often to a point of complete disappearance of all objective manifestations, was the outstanding feature in 9 cases, or in one-third of the group. Most of these patients are under current observa-

tion, they are apparently in good general health and entirely free of subjective symptoms.

In 5 cases the involvement was of an essentially stationary character. These patients presented well established lesions of an apparently chronic type when they first came under observation and have shown no appreciable change during the subsequent follow-up period. It should be pointed out, however, that while these patients have suffered no obvious ill-effects as far as their general health is concerned, they all exhibit organic changes of a permanent nature with consequent functional impairment. Their eventual fate must, therefore, be regarded as uncertain.

A changing character of the disease consisting of alternate periods of progression and regression of the lesions in various localizations was observed in 5 cases. In some of these the clinical picture eventually reached a state of stabilization with varying degree of residual organ involvement, while in others the disease is still of a labile character. This behavior appears to be due to invasion of various organs at successive intervals. It is precisely this type of case which so often defies all attempts to establish a rigid classification of the clinical forms of sarcoidosis.

In the remaining 9 cases the course of the disease was progressive and in 7 of these it was fatal. Of the fatal cases, 3 died of progressive and destructive chronic pulmonary tuberculosis, and in 2 others autopsy revealed disseminated haematogenous tuberculosis of a frankly caseous character. One patient, who during life presented evidence of bacillary pulmonary tuberculosis, died suddenly and the cause of death could not be determined. In the seventh case there were clinical indications of terminal congestive failure, evidently the result of extensive pulmonary involvement of long standing. It may be assumed that the fatal outcome in this case was due to progressive sarcoidosis, although confirmation by autopsy could not be obtained. Thus, of the 7 fatal cases at least 5 showed conclusive evidence of frank tuberculosis of sufficient extent and severity to be regarded as the direct cause of death.

In the light of these observations it would appear that one is not justified in assuming too confident an attitude regarding the ultimate outcome. A definite proportion of the cases will show a most remarkable degree of spontaneous regression of the lesions with apparent recovery, while in a good many others the disease may cause organic involvement of an irreparable character. There are no means of determining the course of the disease in the individual case except by actual observation of its evolution. The prognosis depends largely on the extent of persistent organic changes and on the degree of permanent functional damage resulting from localization of the lesions in particular organs. Some of these localizations, already referred to in preceding paragraphs, need particular emphasis from the standpoint of their prognostic significance. Thus, chronic disability and eventually death may result from extensive pulmonary involvement causing respiratory and cardiac insufficiency. Involvement of the heart proper may likewise result in serious functional impairment and eventual cardiac failure. In some cases localization in the eye causes blindness. Ex-

tensive cutaneous and osseous changes may occasionally lead to considerable outward deformity with mutilation.

Particular consideration must be given to tuberculosis as a factor influencing the eventual fate of sarcoidosis patients. It represents a significant turn in the course of the disease and in this series it was responsible for most of the fatal cases. There is reason to believe that tuberculosis is not merely an incidental complication, but that the potentiality of its development in the course of sarcoidosis is inherent in the nature of this disease. This phase of the problem will be discussed in detail in connection with the pathogenesis.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In the diagnosis of sarcoidosis the clinical picture as a whole must be taken into consideration. While the appearance of the lesions in the individual organs may resemble a variety of other conditions, their peculiar combinations which occur with a certain degree of regularity will often be of material aid in the clinical diagnosis. The presence of cutaneous manifestations and the finding of characteristic changes in the roentgenogram of the bones, in association with visceral involvement, render the diagnosis fairly obvious. Likewise, the combination of lesions in the internal organs with involvement of the eyes and parotid gland should strongly suggest the possibility of systemic sarcoidosis. For a conclusive diagnosis, however, histological examination of biopsy tissue is essential.

Cases with predominantly visceral localization of the disease may present particular diagnostic problems. Because of the frequency of involvement of the lymph nodes and lungs in cases of this type, other conditions causing systemic lymphadenopathy, especially Hodgkin's disease, as well as disseminated forms of tuberculosis, will have to be considered.

Tendency to systemic involvement of the lymph nodes with particular localization in the mediastinal and tracheobronchial regions is a characteristic feature of both Hodgkin's disease and sarcoidosis, although participation of the peripheral nodes is usually less conspicuous in the latter. Splenomegaly is not infrequently found in sarcoidosis, but is as a rule more pronounced in Hodgkin's disease. While pulmonary involvement is much more common in sarcoidosis, the roentgenographic characteristics of the changes cannot be regarded as necessarily typical of this disease. Spontaneous regression, rather frequent in sarcoidosis, is generally not observed in Hodgkin's disease. On the other hand, lymph node involvement due to sarcoid is apparently not influenced by radiation therapy, in contrast to Hodgkin's disease or other types of lymphoblastoma. The practical importance of making an early distinction between these two conditions, both from a prognostic and therapeutic point of view, is quite evident. Biopsy of a superficial lymph node, even though its location and size may appear rather inconspicuous, will often be of decisive aid in the presence of sarcoidosis.

The differentiation from tuberculosis of the haematogenous type may be quite difficult on purely clinical grounds. This applies particularly to the chronic forms of disseminated tuberculosis in which, just as in sarcoidosis, constitutional

signs and symptoms may be either slight or absent. The roentgenographic appearance of the pulmonary changes is often identical in both instances. The lymph node involvement, especially the intrathoracic lymphadenopathy, is both more frequent and more pronounced in sarcoidosis. Tuberculin anergy is an important point against ordinary tuberculosis, while a positive test does not necessarily exclude the possibility of sarcoidosis. Certain localizations considered as characteristic for sarcoidosis and rarely observed in tuberculosis will be of material aid, but conclusive proof of the diagnosis rests with the biopsy findings. In some atypical cases, however, the similarities between sarcoidosis and tuberculosis, both as regards the clinical and pathological findings, may be so close that it would be extremely difficult to establish a clear line of demarcation.

Cases in which marked splenomegaly represents the dominant clinical feature of the disease might be regarded as instances of so-called Banti's disease. The frequent association with other localizations, particularly with involvement of the lungs and lymph nodes, neither of which are features of Banti's syndrome, is of importance in the clinical differentiation. Biopsy will usually establish the diagnosis if sarcoidosis is the cause of the splenomegaly.

That the roentgenological appearance of the pulmonary changes in sarcoidosis may show certain similarities with a number of other conditions, such as silicosis, carcinomatosis or vascular congestion, has been mentioned before. Careful evaluation of the general clinical picture will, as a rule, enable one to eliminate such possibilities from serious consideration.

TREATMENT

There is apparently no effective treatment available for sarcoidosis. A variety of therapeutic agents have been used and varying degrees of success claimed. Arsenicals, tuberculin, ultraviolet rays, X-rays and radium, gold injections, have been recommended at one time or another, either as a general or local measure. There is, however, no convincing evidence that any one of those measures employed can actually alter the course of the disease. Since marked spontaneous regression is a frequent occurrence in sarcoidosis, it is understandable that various results may readily be attributed to treatment if the latter happens to have been employed during a regressive phase.

The disease runs its own, often unpredictable, course apparently uninfluenced by any therapeutic intervention. Treatment can be only supportive and symptomatic. During the active phase, especially when constitutional signs and symptoms are present, rest treatment is, of course, advisable. It should be pointed out, however, that prolonged institutional care is not indicated in cases with lesions of a chronic stationary character, such as in patients with chronic forms of pulmonary involvement, provided that active tuberculosis can be excluded. Many of these cases may be able to pursue a fairly normal life over a period of years. Periodic examinations are, of course, essential in order to follow the evolution of the disease, although it must be admitted that there is little that can be done to prevent the occurrence of serious developments.

SUMMARY

1. A study of 35 cases of sarcoidosis is presented, this part of the report dealing with the clinical observations. In a large proportion of the cases extended follow-up provided an opportunity to study the evolution of the disease through its various phases.

2. The majority of the patients of this series were Negroes, a fact which would tend to confirm the observation that in the United States the disease apparently occurs with considerably greater frequency in Negroes than in white persons.

3. Sarcoidosis is inherently a wide-spread systemic affection with particular predilection for certain organs or anatomical systems. The diverse manifestations of the disease, which have given rise to the establishment of a variety of clinical forms and syndromes, may be regarded as variants of an essentially identical morbid process. The great variability in the clinical picture depends largely on the localization of the lesions in particular organs and their manifold combinations.

4. Visceral localization of the disease, especially involvement of the lungs and lymph nodes, is far more frequent than some of the other localizations considered as more characteristic for sarcoidosis, such as skin and bone lesions. Manifest changes in the lungs and lymph nodes were observed in nearly all of the cases of this series. Involvement of the mediastinal and tracheobronchial lymph nodes represents a significant clinical feature of the disease.

5. Cutaneous lesions were present in 40 per cent, manifest bone changes in about one-fourth of the cases. Localization in the eye and its adenexa, in the spleen and liver, is a fairly frequent occurrence. The relative frequency of organ involvement appears to be greatly influenced by the particular source of selection of the clinical material.

6. Among the outstanding general clinical characteristics of sarcoidosis are its exceedingly chronic protracted course, the frequent disproportion between the extent of the wide-spread anatomical involvement and the apparently good general health of the patient, as well as a pronounced tendency to spontaneous regression of the lesions in various organs.

7. The clinical manifestations resulting from localization of the lesions in the individual organs and their various combinations were discussed.

8. A detailed analysis was presented of the types of pulmonary lesions. The various forms of pulmonary involvement observed in sarcoidosis, similar to those occurring in other organs, may be regarded as expressions of different phases in the dynamic evolution of the disease. A distinction may be made between apparently early and late forms, as well as between regressive, stationary and progressive types.

9. In many cases the presence of characteristic lesions in typical locations will permit a correct clinical diagnosis. In the differential diagnosis of cases with predominant localization in the visceral organs, Hodgkin's disease and disseminated haematogenous forms of tuberculosis deserve particular consideration. For a conclusive diagnosis biopsy is often indispensable in cases of this type.

10. For the evaluation of the course of the disease as a whole and its eventual fate, prolonged observation is essential. In the present series approximately one-third of the cases showed a clearly regressive course with apparent recovery, in one-third the disease was either stationary or periods of remissions alternated with exacerbations and in the remaining one-third the course was of a progressive character. Fatal termination was observed in 7 patients.

11. The prognosis of sarcoidosis depends in a large measure on the extent of permanent and irreparable functional damage resulting from localization of the lesions in certain organs, particularly the lungs, heart and eyes. Development of frank tuberculosis is a significant occurrence influencing the eventual outcome in a definite proportion of the cases.

12. Tuberculosis accounted for most of the fatal cases in the present series. This observation, together with the occurrence of atypical cases occupying a borderline position between sarcoidosis and tuberculosis, indicates a close relationship between these two morbid entities. Transition into ordinary tuberculosis apparently represents a potential development in the course of sarcoidosis. The pathogenetic significance of these findings will be discussed in the second part of this report.

SUMARIO

1. Preséntase el estudio de 35 casos de sarcoidosis, hallándose esta parte del trabajo dedicada a las observaciones clínicas. En una elevada proporción de los casos una larga observación permitió estudiar la evolución de la dolencia en sus varias fases.

2. La mayoría de los enfermos del grupo eran negros, lo cual tiende a confirmar la observación de que en los Estados Unidos la afección se presenta con frecuencia mucho mayor en dicha raza que en la blanca.

3. La sarcoidosis es inherentemente una afección orgánica diseminada que muestra decidida predilección hacia ciertos órganos o aparatos anatómicos. Las diversas manifestaciones del mal, que dan origen al establecimiento de varias formas y síndromes clínicos, pueden ser consideradas como variantes de un procesos morboso en el fondo idéntico. La gran variabilidad del cuadro clínico depende en gran parte de la localización de las lesiones en órganos dados y de sus múltiples combinaciones.

4. La localización visceral, y en particular la invasión de los pulmones y ganglios linfáticos, es mucho más frecuente que algunas de las otras localizaciones consideradas como más típicas de la sarcoidosis, por ej., las cutáneas y las óseas. En casi todos los casos de esta serie observáronse lesiones manifiestas en los pulmones y ganglios linfáticos. La invasión de los ganglios mediastínicos y traqueobronquiales representa una importante característica clínica del mal.

5. En 40% de los casos había lesiones cutáneas y aproximadamente en la cuarta parte alteraciones óseas manifiestas. La localización en el ojo y sus anexos, y en el bazo e hígado es bastante frecuente. En la relativa frecuencia con que se afectan distintos órganos parece influir considerablemente la selección del material clínico y su procedencia.

6. Entre las sobresalientes características clínicas generales de la sarcoidosis figuran: su evolución crónica y por demás prolongada, la frecuente falta de relación entre una invasión anatómica generalizada y la aparente buena salud general del enfermo, así como la pronunciada tendencia a la regresión espontánea de las lesiones en los varios órganos.

7. Repásanse también aquí las manifestaciones clínicas debidas a la localización de las lesiones en distintos órganos y sus varias combinaciones.

8. Ofrécese un análisis detenido de los tipos de las lesiones pulmonares. Las varias formas de invasión pulmonar, semejantes a las observadas en otros órganos, pueden considerarse como expresiones de diversas fases de la evolución dinámica de la dolencia, pudiendo trazarse una distinción entre las formas aparentemente tempranas y las tardías, así como entre las regresivas, las estacionarias y las progresivas (evolutivas).

9. En muchos casos la existencia de lesiones características en sitios típicos permitirá hacer el diagnóstico clínico acertado. En el diagnóstico diferencial de los casos en que predomina la localización visceral hay que tomar muy en cuenta la enfermedad de Hodgkin y las granulias hematógenas, siendo a menudo indispensable la biopsia para el diagnóstico definitivo en los casos de este género.

10. Para la justipreciación de la evolución de la dolencia en conjunto y del pronóstico final, la observación prolongada es de rigor. En la serie actual aproximadamente la tercera parte de los casos mostraron una evolución netamente regresiva acompañada de aparente reposición, en otra tercera parte la enfermedad era estacionaria o alternaban los períodos de remisión con exacerbaciones, y en el resto el mal era del tipo progresivo. En 7 enfermos el desenlace fué fatal.

11. El pronóstico de la sarcoidosis depende en gran parte de la extensión del daño permanente e irreparable que ha producido en la función la localización en ciertos órganos, y en particular los pulmones, corazón y ojos. En una proporción bien definida de los casos la aparición de una tuberculosis declarada es hecho significativo que afecta el desenlace.

12. En la serie aquí estudiada la tuberculosis ocasionó la mayor parte de las muertes, lo cual, unido a la existencia de casos atípicos que ocupan una posición fronteriza entre la sarcoidosis y la tuberculosis, indica cuan íntima es la relación entre esas dos entidades morbosas. En la evolución de la sarcoidosis la transición a una tuberculosis corriente representa aparentemente un desenvolvimiento potencial. En la segunda parte de la comunicación se discutirá el significado patogenético de estos hallazgos.

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GROWTH OF HUMAN TUBERCLE BACILLI UNDER RESTRICTED AIR CONDITIONS[1,2]

MAURICE L. COHN

Growing tubercle bacilli in artificial media requires knowledge of a great many technical features which tax the bacteriologists' erudition, even though, on the face of it, it is extremely simple to grow these bacilli. The problem becomes more involved when conditions under which the bacilli grow are studied. Growth under any planting condition is distinct from growth from very small plantings; and growth on a poor nutrient, relatively speaking, is distinguished from growth on an excellent nutrient from small plantings. The numerous conditions which can influence the growth from small plantings cannot be assumed *a priori* from growth obtained from heavy plantings. Any slight retarding influences in the former case play almost no part in the latter—with heavy plantings and a poor nutrient. Conclusions drawn from the growth of bacilli in heavy plantings on a relatively poor nutrient have led to numerous erroneous deductions in the past. In no case is this more evident than in the influence of air or oxygen tension and in the presence of oils or paraffins used technically.

Corper (1) and Novy (2) studied the effects of low oxygen tension and the effect of other gases on the growth of tubercle bacilli. They used heavy plantings on the standard media of that time, such as nutrient agar or egg media containing retarding dyes. Although their deductions under the conditions of their limited experiments were justified and informative, they did not exhaust the possibilities of present day knowledge and methods of quantitative controlled growth experiments.

Although the human tubercle bacillus is usually considered a strict aerobe, growth below the surface in certain liquid media has been described. Boecker (3) studied growth of tubercle bacilli submerged in liquid media, confirming Besredka's observations, and believed that the high organic phosphorus content of the latter's medium and similar nutritive substrates promoted the utilization of combined oxygen. The experiments, crudely performed with heavy plantings, are inconclusive partly because shaking introduced the factor of uncertain air tension. The purpose of these experiments, obtaining submerged growth, was not confirmed by observations on air tension, which was completely omitted. Likewise, Buc (4, 5) describes aerobic (surface) and anaerobic (under liquid) growth of tubercle bacilli following heavy seedings in effusion fluids and certain organ-containing media as well as under paraffin oils. Too heavy plantings were employed and no estimation of air tensions considered, although he noted decided differences between surface and submerged cultures. Kempner (6) reported on the respiratory metabolism of fifteen to twenty-day old cultures of a human tubercle bacillus (H37) and, contrary to the "all or nothing theory" of cellular respiration, he found the respiration of tubercle bacilli was highly dependent on

[1] From the Research Department, National Jewish Hospital, Denver, Colorado.

[2] This study was aided by the Jacques Labarrere Fund for Tuberculosis Research.

variations of oxygen concentration, expecially in the range of those that actually occur in the body.

Most earlier investigators, however, had no conception of quantitative or immune relations of the tubercle bacillus in tuberculosis nor of the intra- or extravital existence of these bacilli. Drea (7) was the first investigator to perform tests with small numbers of tubercle bacilli in liquid media, using graded quantitative plantings. He used a human strain (H37) and Long's liquid synthetic medium, a relatively poor nutrient but suited to massive growth of surface cultures. He noted submerged growth could be obtained from plants as small as 10^{-7} to 10^{-8} mg. He explained his success and the failure of others on the assumption that very small amounts of contaminating organic substances are easily adsorbed by the glassware and may act as growth inhibitors; and in their presence only plantings of 10^{-2} to 10^{-6} mg. will grow. Soaps, paraffins, distillates from cotton stoppers and metabolic products produced by the growth of tubercle bacilli are incriminated. Their elimination by using new glassware, special cleaning methods and aluminum foil caps resulted in successful growth. His work was concerned exclusively with submerged growth, while our own studies on nutrients for tubercle bacilli have been concerned with all types of growth, considering relative quantities and the relative value of different nutrients. With good nutrients such as the potato, egg-yolk and animal tissues (8), we found that growth occurs regularly in dilutions of 10^{-8} mg. plantings without any special technique to eliminate the inhibitory natural factors suggested by Drea. What concerned us most was making suspensions; and, if the factors suggested by Drea assume importance, it would be necessary to change radically our entire techniques. Therefore, in order to determine more accurately some of the details involved, it appeared essential to check on Drea's observations and compare his techniques with the routine techniques used in our laboratory. The following experiment elucidates this.

In order to compare the results obtained from growing tubercle bacilli as outlined by Drea and as usually performed with the ordinary laboratory techniques, a series of Erlenmeyer flasks (50 cc.) containing 20 cc. of Long's medium was planted with graded amounts of human tubercle bacilli (H37, the same culture used by Drea). Part of these were covered with aluminum foil as directed by Drea and the others were stoppered in the usual fashion with paraffined cotton plugs. After planting, the flasks were then incubated at 37° C. and the results read at regular intervals. The final tabulation is presented in table 1.

The results recorded in table 1 indicate that with the heavier plantings no difference is noted between the growth or time of growth when the glassware specially prepared according to Drea and aluminum foil cover were used or when the ordinary paraffined cotton stoppers were used. However, with the planting of smaller amounts of fine suspension (0.000,1 or 0,000,001 mg.), a definite retardation occurred in the time and amount of growth obtained by the paraffin-cotton-stopper method, as compared with the special Drea method (see figure 1). In order to elucidate the latter effect further, the following experiment was performed. It has been our custom for a number of years to use screw cap

(cork innerlined) bottles (10) for growing liquid cultures of tubercle bacilli on simple nonprotein synthetic media without the use of paraffin. This method presented an opportunity to check the findings by the Drea method. The glassware (bottles) in one series was specially prepared by the Drea method with Drea planting; in another series, it was routinely prepared with routine planting; in the third series, the bottles prepared by the Drea method were planted with routinely prepared suspensions; and in the fourth series, routinely prepared bottles were planted with suspensions made according to the Drea technique. The results obtained within nine weeks at 37° C. incubation are recorded in table 2.

The results recorded in table 2 indicate that the findings recorded in table 1 are accounted for primarily by the use of paraffin applied to the cotton stopper.

TABLE 1

A comparison of the growth of human tubercle bacilli (H37) (9) on Long's medium by standard and Drea techniques

CONCENTRATION OF BACILLI IN MG. PER CC. PLANTED	METHODS USED					
	Drea's specially prepared glasswares and aluminum cover			Standard paraffined stoppered with old glassware		
Lumps (surface planting)		2S	++++*		2S	++++
0.01 (fine suspension)	2U	3S	++++	2U	4S	++++
0.000,1 (fine suspension)	3U	4S	++	6^{2}U		
0.000,001 (fine suspension)	4U			7^{1}U		

*S = surface growth graded from 0 to ++++ since definite gradations occur.

U = submerged growth (never exceeding + so were not graded).

Numeral indicates the number of weeks after which growth of the type indicated first appeared and the exponent when used indicates the number of flasks, of 3 seeded, which yielded growth when all were not positive. The final readings were made after nine weeks of incubation.

With the substitution of a metal cap, cork innerlined, the other features of preparation appear to be of no importance since all the results of the four different series recorded in table 2 are about identical. It is also noted from Drea's report that contaminating materials which cause retardation of growth are to be classed as surface-active agents. For this reason, we measured the surface tension of the media and found that there was a perceptible difference when paraffin was used and when it was avoided. The creeping tendencies of paraffin and paraffin oil are too well known to require further elucidation here, except to note that light films of the paraffins are frequently visible to the naked eye on the surface of liquid media and only exacting experiments disclose their retarding effect on certain plantings. In previous experiments with good nutrients and solid media, using graded plantings, the paraffined cotton stopper did not prove sufficiently retarding to growth to merit serious consideration, such as might be involved in a poor nutrient liquid medium. As a matter of fact, the fatty constituents of egg-yolk did not act as a deterrent to growth and thus

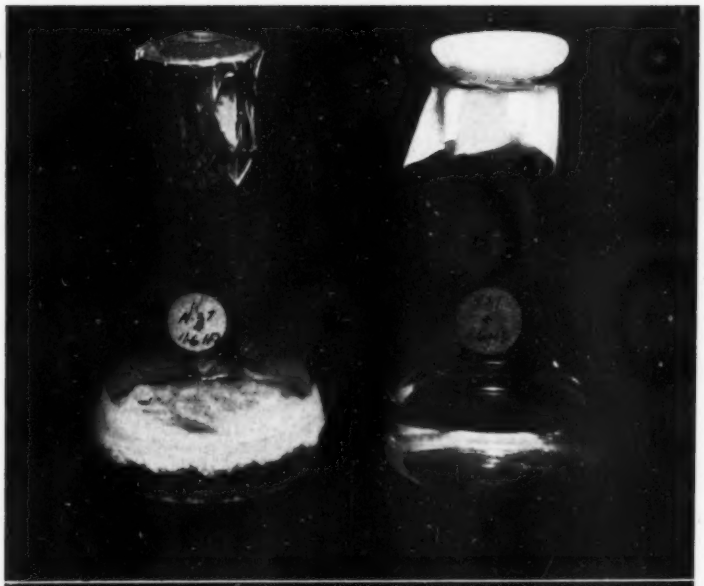

FIG. 1

FIG. 2

FIG. 1. The growth of 0.0001 mg. human tubercle bacilli (H37) in fine suspension on Long's nonprotein synthetic medium, nine weeks at incubator temperature (37°C.); left, capped with aluminum foil and flask specially prepared (according to Drea); right, capped with paraffined cloth and paraffin cotton stopper. Note sparse submerged growth when paraffin was used and good surface and some submerged growth when aluminum cap was used.

FIG. 2. Growth limit of human tubercle bacilli on glycerol broth agar after thirty-five days at 37°C. Left to right: *1*. medium planted with 1 mg. fine suspension in specially cleaned tube with metal cap, cork innerlined; *2*. a similar tube of medium planted with 0.01 mg. fine suspension; *3*. routinely prepared tube of medium planted with 1 mg. fine suspension; and *4*. routinely prepared tube of medium planted with 0.01 mg. fine suspension. Note good growth with heavy planting (1 mg.) in *1* and *3* and absence of growth with smaller planting in *2* and *4*.

FIG. 3. A comparison of the growth of human tubercle bacilli planted in graded amounts on Long's synthetic nonprotein medium in glassware specially prepared and routinely cleaned and stoppered with cork innerlined metal cap and incubated thirty-seven days at 37°C. Left to right: *1*. 0.01 mg. fine suspension planting in specially prepared glassware; *2*. 0.000,1 mg. in specially prepared glassware; *3*. 0.000,001 mg. in specially prepared glassware; *4*. 0.01 mg. fine suspension planting in routine glassware; *5*. 0.000,1 mg. in routine glassware; and *6*. 0.000,001 mg. in routine glassware. Note there is no appreciable difference between the growth in *1* and *4*, *2* and *5*, and *3* and *6*. In *2*, *3*, *5* and *6* a sparse submerged growth is noted on the bottom of bottle; while in *1* and *4*, a veil-like surface growth was also obtained in thirty-seven days with fine suspension planting.

TABLE 2

An analysis of the factors involved in the technique of growing human tubercle bacilli (H37) on a liquid synthetic nonprotein medium (Long's)

METHOD USED	MILLIGRAMS PER CC. OF BACILLI USED FOR PLANTING		
	0.01	0.000,1	0.000,001
Drea's specially prepared glassware and planting	3U 5S ++++*	3U 6S ++	5U 7S +
Routinely prepared glassware and planting	3U 5S ++++	3U 6S ++	5U 7S +
Drea's specially prepared bottles, routinely prepared suspensions	3U 5S ++++	3U 6S ++	5U 7S +
Routinely prepared bottles, Drea's specially prepared glassware for suspension	3U 5S ++++	3U 6S ++	5U 7S +

* The numeral preceding the U or the S indicates the number of weeks at which growth appeared.

U = submerged growth.

S = surface growth.

The amount of growth is designated from 0 to ++++.

prevent its being classed as an excellent nutrient for the growth of small numbers of tubercle bacilli.

The pure paraffins in small amounts display no direct retarding effect on the growth of tubercle bacilli, however they may act indirectly. In submerged cultures particularly they may retard air or oxygen exchange which becomes especially important in deep layers of liquid and sediment growth of bacilli. In order

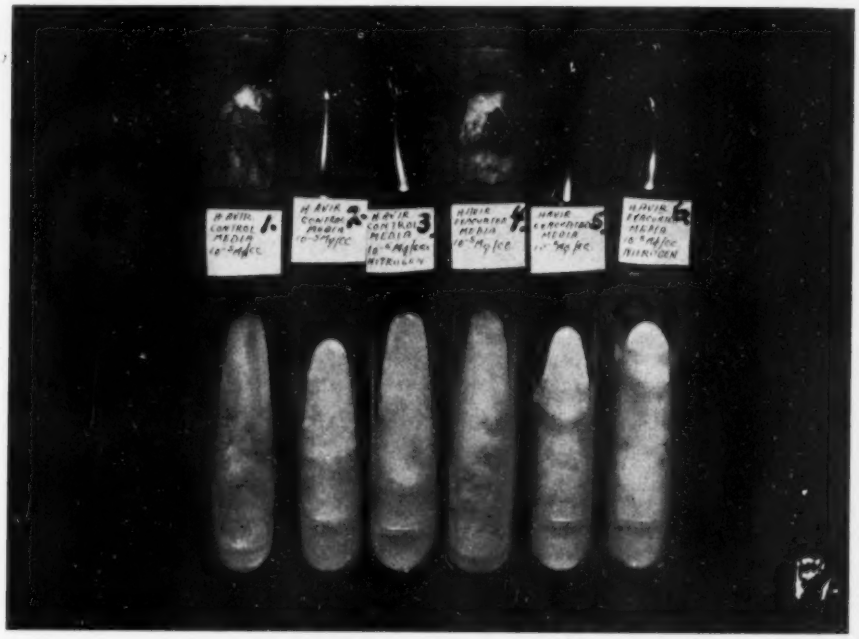

FIG. 4. The growth of small plantings (0.000,01 mg. in fine suspension) of human tubercle bacilli after ten weeks' incubation under restricted air conditions on a good nutrient medium (inspissated egg-yolk). Left to right: *1*. normal growth with paraffined cotton plug and cork stopper; *2*. restricted growth (note small colonies behind film on glass which could not be cleaned before photographing) in glass sealed tube with contained air; *3*. restricted growth, small flat, barely perceptible colonies, when tube was filled with nitrogen and sealed; *4*. similar to tube *1* except air was evacuated from medium before inspissation; *5*. similar to tube *2*, except air was evacuated from medium before inspissation; and tube *6*. similar to tube *3* except air was evacuated from medium before inspissation. Note similarity of growth in tubes *1* and *4*, *2* and *5*, and in *3* and *6*, indicating that evacuating air from medium played no part in the growth of the bacilli.

to elucidate this phase, a study of the oxygen requirements of the tubercle bacilli was made. In the first experiment, a series of tubes of inspissated egg-yolk medium was planted with graded amounts of fine suspensions of tubercle bacilli and glass sealed without any effort to remove such air as may be present normally in the medium or tube. The noteworthy results of such a test were that with heavy plantings (0.01 mg.) growth was barely visible; while with small plantings (0.000,01 mg.) a definitely visible, though not heavy, growth occurred (see figure 4). The explanation was that the heavier plantings contained sufficient bacilli

to exhaust the available oxygen supply while the oxygen supply was adequate to permit concentrated growth of the lighter plantings in restricted areas of a few colonies. In order to carry this analogy further, the growth of the fine planting (0.000,01 mg.) was studied under conditions of (*a*) air exhausted medium, obtained by placing the medium under a vacuum for about four hours before inspissation; and (*b*) after exhausting the air from the medium, an inert gas, nitrogen, was used to fill the tubes. The results of these experiments were that very slight growth still occurred, which could only be explained either by the fact that the bacilli were able to obtain sufficient oxygen from the medium or that our technique was not adequate to prevent a slight oxygen retention in the nitrogen gas in spite of every chemical precaution to remove it. In some experiments, the nitrogen had been passed over hot copper gauze and through sodium pyrogallate solutions in others to remove small amounts of oxygen. When similar tubes were glass-sealed under a vacuum of about 4 mm. of mercury, no growth occurred.

It is evident from the foregoing experiments that the oxygen requirements for sparse growth on a good nutrient medium such as egg-yolk is apparently very small and may throw some light on possibilities of intravital cellular survival in the body. They stress again the significance of oxygen or air in infection as pointed out previously by Corper, Novy and more recently Rich and Follis (11). This problem, however, is involved by profound technical difficulties. It is also obvious that the bacilli grow best with a plentiful supply of air and are relatively retarded *in vitro* by its absence, such as occurs with various grades of liquid submersion or oily protection (12).

SUMMARY AND CONCLUSIONS

The growth of submerged tubercle bacilli in nonprotein liquid media is usually sparse and is affected appreciably by any factors or influences which retard the ready exchange of air or oxygen into the medium. Such effects may be particularly significant when growing tubercle bacilli submerged in a poor nutrient liquid medium but play very little part when growing them on the surface of a particularly good nutrient medium for small plantings, such as are used for diagnostic culture.

The retarding effects noted when growing submerged cultures in a liquid nonprotein synthetic medium and using paraffined cotton stoppers are caused by the use of paraffin rather than any particular method of cleaning the glassware or preparing suspensions of the tubercle bacilli. The tubercle bacillus is an aerobe primarily and therefore grows best *in vitro* with a plentiful supply of air (oxygen). It is capable of sparse growth in almost air (oxygen) exhausted surroundings on a good nutrient such as egg-yolk but will not grow under the conditions of a fairly good vacuum (about 1/100 atmosphere).

Although it has not been proved in these experiments that human tubercle bacilli can utilize other than free oxygen, it is shown that multiplication of the bacilli can occur under extreme conditions of oxygen privation when a good nutrient medium is used.

SUMARIO Y CONCLUSIONES

Las colonias de bacilos tuberculosos sumergidos en un medio líquido sin proteína suelen ser escasas y se ven afectadas apreciablemente por todo factor que retarde la fácil penetración del aire u oxígeno en el medio. Ese efecto puede revestir bastante importancia al cultivar bacilos tuberculosos sumergidos en un medio líquido poco nutriente, pero desempeña muy poco papel al cultivarlos en la superficie de un medio nutriente muy bueno para pequeñas siembras, tal como el empleado para los cultivos destinados al diagnóstico.

El retardo observado al cultivar colonias sumergidas en un medio líquido sintético sin proteína y utilizar tapones de algodón parafinado, procede del empleo de la parafina más bien que de ninguna técnica dada usada para limpiar la cristalería o para preparar suspensiones de los bacilos tuberculosos. El bacilo tuberculoso es primordialmente aerobio y por lo tanto prolifera mejor *in vitro* cuando hay un abasto abundante de aire (oxígeno), si cuenta con un nutriente bueno tal como la yema de huevo, pero no proliferará en un vacío bastante perfecto (aproximadamente $\frac{1}{100}$ de la atmósfera).

Aunque no se ha demostrado en estos experimentos que los bacilos tuberculosos humanos puedan utilizar oxígeno que no sea libre, se observó multiplicación cuando la privación de oxígeno era casi absoluta, si se disponía de un buen medio nutriente.

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BOOKS

MARIO WAISSMANN: *Tuberculosis congenita. Pp. 170, with many illustrations, "El Ateneo," Buenos Aires, 1942, paper.*

By HUGO BEHM

The problem of congenital tuberculosis is discussed, based on a series of 11 cases, which, according to the author, is the largest hitherto reported by one individual. Both the transmission of tubercle bacilli and the heredity of a particular susceptibility have been theoretically accepted in congenital tuberculosis. The inheritance of the tubercle bacillus through the germinal cells is an exceptional contingency without any practical significance. The foetal contamination is, on the other hand, a proved eventuality which may be produced by a bronchial aspiration of the infected amniotic fluid or by a transplacental haematogenous infection. In the first case, the amniotic fluid is contaminated by a tuberculosis of the placenta. Yet it has been discussed that this amniotic infection may originate even in the absence of any placental tuberculosis. Still it is not an easy question to establish that the placenta is not involved, even with an exhaustive microscopical examination. The aspiration of amniotic fluid is possible not only during delivery, but during pregnancy, according to Snyder and Rosenfeld, who are of the opinion that the foetus breathes normally for the last third of its intrauterine life.

The author calls attention to the fact that the formation of a primary complex in the lungs, which has been considered as a characteristic feature of the tuberculosis by aspiration, may also be observed in the transplacental haematogenous tuberculosis. In other words, there are cases of tuberculosis which clearly originated by transplacental haematogenous infection and which present a primary pulmonary tuberculosis without the primary hepatic lesions that are typical of this type of infection. As this problem is intimately connected with the anatomy of the foetal blood circulation, the author made an anatomical and radiological study of this subject. This study showed that there is a course along which blood can flow from the umbilical vein to the lungs of the foetus. This course is made up by Arantius' duct, the inferior caval vein, the right auricle, the orifice of Botalli and the bronchial arteries. This course allows the haematogenous infection of the lungs without previous hepatic lesions; consequently the location of congenital tuberculosis in the lungs does not prove that it is a tuberculosis by bronchial aspiration. On the contrary, the author thinks that most of the cases of foetal tuberculosis are of transplacental haematogenous origin. This is most probable if we take into account that the pulmonary blood circulation is very active from the third month of life on. This same anatomical research showed that Arantius' duct puts off a direct branch to the spleen, which explains the splenic tuberculosis found in these same cases.

This matter is also related with the tuberculosis of the placenta. This tuberculosis is frequently present in the course of pulmonary tuberculosis of the preg-

nant woman, chiefly in serious cases. The frequency of tuberculosis of the placenta is about 40 per cent according to different writers. Yet this does not necessarily imply the infection of the foetus, as the placenta acts in a certain way as a filter against the tubercle bacillus.

Nothing has proved hitherto Baumgarten's idea that tubercle bacilli are kept latent in the child, which are to give birth to pulmonary tuberculosis in adult life. On the contrary, the results were quite negative in a careful investigation, both anatomical and bacteriological, made by Lelong on 15 children whose death was caused by nontuberculous diseases and who were born of tuberculous mothers. The transmission of ultravirus has been also wholly disregarded.

As to inherited disposition, on which Curveilleur insisted so much, the author's experience shows that the development of children born of tuberculous mothers and isolated from their parent is perfectly normal. Nobody has proved that the transmission of antibodies from the mother into her child means inherited immunity for the latter. On the contrary, experiments carried out by Lurie on rabbits show that it is the inheritance of a determined genetic constitution which decides the susceptibility or the resistance to the infection.

The author reports 11 cases of congenital tuberculosis found in examining 737 children of tuberculous mothers, that is, an incidence of 1.46 per cent. But autopsy was not systematically performed on every one of these children. The organization of the Department where that research was made permits a perfect isolation of the children from the very moment of their birth, and thus every possibility of after-birth infection is eliminated. The highest frequency of congenital tuberculosis was found in premature children born of mothers with far advanced pulmonary tuberculosis (9.5 per cent). It is also frequent in children born at full term of mothers who died in the course of delivery due to far advanced tuberculosis (7.35 per cent). At the autopsy of these cases every sort of disseminated tuberculous lesion was found, principally in the lungs, liver and spleen. These lesions were typical miliary tuberculosis or disseminated caseous foci, mainly in the lungs, and frequent caseous involvement of the mediastinal lymph nodes. Only 2 of these cases were recorded as produced by bronchial aspiration, and all the rest as transplacental haematogenous infection.

The author states that the conditions usually expected in cases of congenital tuberculosis do not necessarily present themselves always, and that the only rule to follow is to eliminate wholly the possibility of an after-birth infection. On the other hand, it is not true either that congenitally infected children are bound to die soon, because some of them have survived for thirty weeks.

Finally, the author draws attention to the fact that congenital tuberculosis is not unusual but comparatively frequent, mainly in far advanced tuberculosis of the mother, according to his own statistics. Congenital tuberculosis has also been described in cases where the mother was suffering a not very serious tuberculosis.

Waissmann's book represents a valuable contribution to the study of human congenital tuberculosis. Its principal importance lies in its demonstration that this tuberculosis is of a comparatively high frequency in cases of far advanced

pulmonary tuberculosis of the mother. From this fact we must conclude that the pregnancy of a woman with an active pulmonary tuberculosis must be systematically interrupted at an early stage.

The Hospital in Modern Society. Edited by Arthur C. Bachmeyer and Gerhard Hartman. Pp. xiv + 768, New York, The Commonwealth Fund, 1943, cloth, $5.00.

By E. M. BLUESTONE

This compilation fills a long-felt need. The literature on hospital administration has not kept pace with the high scientific traditions of medical journalism and the contributions having permanent value in this field have therefore been comparatively few. We owe a debt of gratitude to the editors for the preparation of this volume of selected readings in hospital administration. At a single stroke, they have shown how much can be accomplished by a more profound interest in the literature of hospitalization. On the whole, their selections have been dictated by a strong sense of responsibility to the specialty of administrative medicine. For the mature executive, as well as for the apprentice, and for the socially-minded physician, philanthropist and hospital worker, this attractive omnibus is a boon. One can turn to almost any page and find something stimulating to read.

Among the contributors, the late Dr. S. S. Goldwater is quite properly in the lead with nine articles. He was, indeed, the genius of the modern hospital and the most gifted as well as the most influential member of the literary set among his contemporaries. It is to be regretted that the editors discontinued their search for good material three years before the publication of this volume but, on the other hand, it is to be hoped that a second volume will be forthcoming to cover not only this period, but also some excellent examples of earlier hospital literature which may have been omitted here for lack of space. To some degree, a striking weakness in the writings of hospital executives has been corrected in these pages by the bibliography which appears at the end of each section. While it cannot be claimed that these short bibliographies are complete, they are at least helpful and open up literary fields which the reader may explore at his convenience.

There will be differences of opinion as to the wisdom of some of the selections which go to make up this collection. In the opinion of one reader at least, the editors might have done better if they had consulted each author to compare preferences. If this had been done, a number of classic articles from the pens of several creative writers in the field, who are in the best possible position to judge literary values, would have been included. More space might have been assigned to the views of competent observers in the field of mental disease, tuberculosis and chronic disease generally. The pharmacy section is thin and the subject of rehabilitation, which projects the hospital into the new era, passes almost unnoticed. Public and proprietary hospitals are kept at arm's length.

This book appears during a transition period and some readers will therefore wish that one of the veteran writers in the field of the modern hospital, bold enough to look into the future, had been included. Most readers, however, will not be disturbed by minor shortcomings and will welcome this volume for the excellent reading material which it has brought together. It meets a very severe test in that it makes the reader long for more.

Untapped Manpower. Facts and Figures on Employment of the Physically Handicapped. Pp. 15, United States Civil Service Commission, Washington, D. C., August, 1943, paper.

By LOUIS E. SILTZBACH

This concise booklet is an exhortation and a guide. It urges judicious employment of three million physically handicapped workers who are available in this country now. Among them are returning disabled war veterans. Although the pamphlet is addressed to appointing officials of the various federal agencies, its facts and figures should interest all those who deal with the handicapped, in business, industry and welfare agencies. It will set physicians thinking about new employment opportunities for their disabled patients.

The physician has a part in the intelligent placement of the handicapped. He assesses the physical capacities of the individual. These are matched against the demands of the specific job, very few of which call for all the normal endowments. Indeed, a physical handicap may become an asset; the employee with limited or no hearing is more efficient at noisy jobs and is preferred by many employers.

Accumulated experience shows that the physically handicapped, as a group, are productive and highly efficient. Their attendance and tardiness records are better than those of the able-bodied and they stick to the job. They are alert and careful, hence they have fewer accidents. Those things are true whether the disability be orthopedic, visual, auditory, cardiac or a tuberculous one. The United States Civil Service Commission's recent *Manual for Placement of the Physically Handicapped* reduced the guesswork which has hindered placement of the handicapped. This little pamphlet clears away more brush.

WILEY D. FORBUS: *Reaction to Injury. Pathology for Students of Disease Based on the Functional and Morphological Responses of Tissues to Injurious Agents. Pp. 797, with 532 illustrations, 20 of which are in color, Baltimore, The Williams & Wilkins Company, 1943, cloth $9.00*

By AARON EDWIN MARGULIS

Many excellent textbooks of pathology in English are currently available. The writing and publication of a new text requires a high degree of courage, broad

knowledge, and the expenditure of a vast amount of energy. To justify these, it must embody a new contribution.

The new contribution can hardly be in the nature of new data. This would certainly not be the function of a textbook. This can only be a more concise abridgement, a more definitive and encyclopedic treatment, a fresh principle of pedagogy or a more illuminating sequence of presentation. It can be stated at the outset that Doctor Forbus has significantly enriched the pathological literature by undertaking and partially completing this project. It fulfills teaching requirements of presenting an adequate amount of factual material in a stimulating and consistent way.

This book illustrates again, that the whole is greater than the sum of its parts. The plan of the book, ambitious and somewhat novel, is not entirely new, yet it has been carried out in bolder spirit and to greater completion than heretofore. The data relative to the various aspects of disease, whether of clinical, physiological, pathogenetic, or of pathological-anatomical nature, can, taken individually, be found in greater completeness in textbooks of medicine, of physiology, in definitive texts of pathological anatomy, and so on. But within the confines of these 800 pages will be found a more complete integration of these elements in delineation of the natural history of specific diseases, and a more illuminating analysis of basic pathological reactions than in comparable texts extant.

This work of Doctor Forbus', of which the present volume is but the first half, is intended as a text of sufficient comprehensiveness to serve the needs of students and "young doctors of medicine." But the exposition of the facts of pathology is neither the sole nor the primary consideration. The central interest is directed to the introduction of order into an essentially chaotic mass of accumulated data, that is, the presentation of the subject matter of pathology as the *basic science* of disease in the conventional meaning of this term. This is an aspect that many texts either ignore or treat as an appendage ("general pathology") to an enumerative treatment of "special pathology."

Doctor Forbus approaches pathology in the spirit of a Linnaen systematist. This is indeed an "anatomy" of pathology. Doctor Forbus' primary assumption is that disease is reaction to injury, and that such reaction can be classified into three broad groups: (*1*) resistive, (*2*) submissive, (*3*) adaptive. Under these three basic reaction types are systematically distributed all pathological reactions. This present volume includes only the resistive reaction, principally the inflammatory process and the infectious diseases that arise therefrom. A succeeding volume will undertake the discussion of the other two types of reaction.

This first volume has two major divisions. In part one (123 pages), labelled *Introduction to the Study of Disease*, there are chapters on the general scope of pathology and its relation to other medical disciplines, and on the evolution of present day conceptions of the nature of disease, and its causation, which are treated in greater detail and in broader viewpoint than are available in similar textbooks. These chapters are interesting and stimulating, and may well instill attitudes and a general comprehension that can outlast (and usefully!) inevitably fading memories of specific details of pathological anatomy.

Part two (648 pages) treats in detail of the resistive reaction. The sub-

divisions are systematic outlines of the various patterns of inflammatory reactions, and under each are grouped various infectious diseases as illustrative examples of the general principle.

This might imply that the discussion of particular diseases is merely a subsidiary matter. This is not true. Sections on each disease can be read independently, and one will find excellent summaries of its aetiology, pathogenesis, and adequate description of the anatomy of its lesions, and often the origin of symptoms. There is especially full treatment of the viral, ricketsial and fungal infections. But there is never loss of the primary interest in the individual as a "mass of integrated reacting cells, tissues and organs."

The style is lucid and readable, though not often distinguished. The presentation is exceptionally well organized. The format is pleasing, and there is a profusion (532 figures, many in color) of excellent illustrations.

Many critical statements might be made about this book, but one ventures to predict that the book as a whole will surpass any criticism levelled upon it. Anyone interested in a restricted field can find in a book of this size, within the description of that field, errors of fact and mistakes in interpretation. This is true of the discussions of tuberculosis and other diseases of the lungs. But these, with a few exceptions, are of the nature of trivia and do not vitiate the presentation. One might criticize the extent to which systemization has been carried out, resulting in subsection headings formidable in phraseology and not always understandable without further explanatory details. But this effort, though its bald outline may appear complex, is essentially in the direction of logical simplification. Dr. William Boyd has somewhere stated that systematists can be divided into two groups, the "lumpers" and the "splitters." This book illustrates that "lumping" and "splitting" are not necessarily antithetical. Analysis must proceed and illuminate synthesis. To grasp the significance of a logical simplification may require a sustained effort on the part of the student. A mere ennunciation of the final simple principles that emerge might lead only to repetitive verbalization, while the apprehension of the complex structure that these support and order can leave only a feeling of intellectual joy.

Some day a new type of text in pathology will be written. It might be a slim book of no more than several hundred pages. It might not contain a detailed description of any particular nosological entity. But it might present the subject of pathology as a basic science in the same way that it is possible to present the elements of thermodynamics without a delineation of the thermodynamics of any particular system. It would treat not of the distinctions between diseases but of the similar elements (causative and reactive) in all disease processes. Certainly one could make a list of the changes that occur in cells and tissues and such a list would neither be very long nor very formidable. And yet it is but the combinations and permutations of these that are segregated into tens of scores of names and eponyms. This book is not such an achievement. But in the very bulk of its ordered analysis it is a step toward that desirable goal.

Brief Comment

Tuberculosis in the United States. Graphic Presentation. Mortality Statistics for States and Geographic Divisions by Age, Sex and Race. Prepared by the staffs of the Division of Public Health Methods, National Institute of Health, and the Tuberculosis Control Section, States Relations Division, U. S. Public Health Service, under the direction of Carroll E. Palmer, M.D. Medical Research Committee, National Tuberculosis Association, 1943, paper.

In order to point out to the reader the importance of this most interesting and useful publication, the reviewer can do no better than to quote the major portions of the Foreword:

"This volume is the first in a series presenting in graphic and tabular form factual data about tuberculosis. It is the result of a cooperative undertaking by the National Tuberculosis Association and the United States Public Health Service.

"The purpose of this series is to assemble, analyze, and present in a uniform way statistics about tuberculosis for geographic areas and political subdivisions of the country. It is an attempt to meet a definite need in the field for a convenient source of reference for indices and measurements of the status of and changes in the tuberculosis problem. Such a source of reference, useful as it is in time of peace, becomes of even greater value in time of war, when great industrial and social changes create special problems in tuberculosis and its control. This series of volumes will, it is hoped, provide both a needed source of reference and base lines for evaluating the special problems created by the war. It should also be useful as a guide for the planning of control programs, and contribute to a better understanding of the epidemiology of tuberculosis."

"The present volume contains three charts and one table for: (a) The United States, (b) each State, and (c) each geographic division. The table contains, for each of the three-year periods, 1919-1921, 1929-1931, and 1939-1941, basic data on population, deaths from tuberculosis, and death rates for tuberculosis, by age, sex, and race. The charts present for each area:

1. Tuberculosis mortality by age, average annual rates by sex and color, 1939-1941.
2. Tuberculosis mortality for three decades, by age; average annual rate, 1919-1921, 1929-1931, and 1939-1941.
3. Tuberculosis deaths by age and by sex, percentage distribution for white and for nonwhite, 1939-1941.

"The charts are identified by serial numbers consisting of two pairs of digits. The first pair designates serially the type of chart; the second pair identifies the State (the first digit selecting the geographic division). When separate charts are presented for whites and for nonwhites the letters W and N respectively, are added to the serial number.

"The data for this volume were made available through the cooperation of the United States Bureau of the Census. Mortality data are on the so-called 'recorded' basis, that is, they represent deaths registered as having occurred

in a given locality. For most states the number of 'recorded' deaths differs very little from the number of 'resident' deaths; that is, those of residents of the State, irrespective of the place of occurrence of death. For only four States (Arizona, Colorado, New Mexico, and North Carolina) and the District of Columbia are the differences between resident and recorded figures as great as 10 per cent. The mortality data relate to all forms of tuberculosis and cover 3-year periods centering at the census years. The enumerated populations of the censuses of 1920, 1930, and 1940 are used."

"Statistics by race are presented in two classifications: white and nonwhite. The latter group consists in large part of Negroes (about 95 per cent) with minor proportions of Indians, Chinese, Japanese, and other races. Mexicans are included with 'white.' "

The two agencies which have pooled their resources to make this publication possible have earned the sincere gratitude of many workers. The succeeding volumes in this series are anticipated with deep interest.

IAGO GALDSTON: *Behind the Sulfa Drugs. A Short History of Chemotherapy. With a preface by Perrin H. Long. Pp. 174, D. Appleton-Century Company, New York, London, 1943, cloth, $2.00.*

Doctor Galdston's book is of twofold importance: (*1*) He has written, in lucid and graceful style, the story of chemotherapy, easily understandable for the layman. Incidentally, it will add historical and genetic understanding to the knowledge which the practicing physician may have acquired through current medical literature. (*2*) He presents an excellent example of writing which is popular without being vulgar, a story which is of consuming interest without being overdramatized and distorted. He achieves these effects by elevating his lay audience to his level of scientific, but nontechnical accuracy, instead of descending in form and content to the lowest mental level of his expected audience. We are sorely in need of this type of honest and dignified popularization, while the market is swamped with popular books and papers for the layman in which spectacular effects are achieved by cheap means of Hollywoodish dramatic embellishments. That Doctor Galdston's book will inform and please the layman (and many physicians who want to know more than the practical application of the latest sulfa-drugs) is certain; that, by example, it will help to teach the proper methods of scientific instruction of the lay public, is a fervent hope.

Books Received

HARRY J. BAKER: Introduction to Exceptional Children. Pp. xiv + 496, New York, The Macmillan Company, 1944, cloth, $3.50.

WILLIAM ARKWRIGHT DOPPLER: Tuberculosis—Labor and Management. A Guide to Industrial Relations. Pp. 52, published by National Tuberculosis Association, 1790 Broadway, New York 19, N. Y., 1944, paper, twenty-five cents.

LEOPOLD LICHTWITZ: Pathology and Therapy of Rheumatic Fever. With Foreword by William J. Maloney. Edited by Major William Chester, M.C. Pp. xvii + 211, with 69 illustrations, New York, Grune & Stratton, Inc., 1944, fabrikoid, $4.75.

Medical Radiographic Technic. Prepared by the Technical Service Department of General Electric X-ray Corporation, under the editorial supervision of Glenn W. Files, Director, in association with 17 contributors. Pp. 365, with 381 figures, Charles C. Thomas, Publisher, Springfield, Illinois—Baltimore, Maryland, 1943, fabrikoid, $6.00.

The Health of Children in Occupied Europe. Pp. 37, International Labour Office, Montreal, 1943, paper, twenty-five cents.

AMERICAN TRUDEAU SOCIETY

Report of Meeting of Eastern Section on January 21, 1944

Dr. James C. Walsh, *Secretary-Treasurer*

The Eastern Section of the American Trudeau Society held a meeting at the Pennsylvania Hotel, New York City, Friday, January 21, 1944, jointly with the Tuberculosis Sanatorium Conference of Metropolitan New York. There were over 500 members and guests present.

The Chairman, Victor Cullen, M.D., presided. Morning, afternoon and evening sessions were held. The following officers were selected for 1944.

Chairman	Olin S. Pettingil, M.D. Middletown, Massachusetts
Vice-Chairman	James C. Walsh, M.D. Farmingdale, Long Island
Secretary-Treasurer	N. Stanley Lincoln, M.D. Mount Morris, New York

The papers presented at the Scientific Session were as follows:

Morning Session

Fluorescence Microscopy of the Tubercle Bacillus by Clarence F. Graham, M.D., Hermann Biggs Memorial Hospital, Ithaca, New York.

The speaker outlined the technique, which consists in staining the fixed smear for two minutes or longer with a fresh saturated aqueous solution of auramine-O, followed by decolorization and counterstaining for thirty seconds with standard Gabbett's solution—2 per cent methylene blue in 25 per cent aqueous sulphuric acid. He emphasized that the absolutely essential requirement of the whole method is a powerful light source and recommended the use of a 500 watt projection bulb in connection with a pair of 4 inch diameter plano-convex lenses to concentrate the light on the microscope mirror.

The light is filtered through a solution of copper sulphate and ammonia in a flat-sided museum jar and the strength of the solution is adjusted by the darkness of the microscope field. A yellow ocular disc is used in the eyepiece of the microscope and many types of yellow glass are available for this purpose.

Results of parallel examinations by the Ziehl-Neelsen and the fluorescence method were reported for a series of 1,019 examinations from the Biggs Memorial Hospital. Practically all specimens were from patients known to have been tuberculous at one time or another. The fluorescence method yielded 18.2 per cent more positive results than the Ziehl-Neelsen method in the borderline cases where only a few organisms were discovered. The figures were only preliminary since the tabulation was not yet complete.

The Fate of Infants or Very Young Children with Tuberculosis by Henry S. Willis, M.D., Wm. H. Maybury Sanatorium, Northville, Michigan and Gertrude F. Mitchell, M.D., Detroit, Michigan.

Tuberculosis is well known to produce a high mortality in the very young. Data on hospitalization, discharge and follow-up of 243 children below three years of age in the Maybury Sanatorium indicate that prompt and continued hospitalization is helpful in returning such children to normal health.

In any large community, especially an urban community, there are, all told, a considerable number of children in whom tuberculosis produces definite pulmonary lesions. The larger number of these are of the primary type but a considerable sprinkling of reinfection type lesions occurs. Some of these lesions are very extensive. The data presented in this study indicate that the children of the group who were kept in the hospital until the disease was under quite satisfactory control fared better than those who left the hospital before their disease could be so classified. The overall picture appears to indicate that hospitalization is decidedly beneficial.

Follow-up extended over a considerable time, the shortest being six months, the longest seventeen years. Among the 153 primary cases who were followed after discharge, 142 were regarded as clinically well, one had been readmitted to the hospital and 10 had died.

X-ray Studies of Atypical Pneumonia by E. C. Showacre, M.D., Cornell University, Ithaca, New York.

X-ray studies in atypical pneumonia was a presentation of sets of serial radiographs from the Cornell University Infirmary, demonstrating the onset, development, secondary spreads and the recession of this disease from the radiographic viewpoint.

Abnormal shadows were present in most at thirty-six hours following onset of symptoms but some appeared as early as twelve hours and others as late as seven days. Most lesions appeared first in the hilar area and extended outward but the reverse was not uncommon. Densities varied from a homogeneous haze to fine soft nodules, usually attaining their maximum fan or band shape in one week. Recession began then unless a spread had occurred.

One type of spread was of an explosive type, involving large areas of the lung similar to wide-spread bronchopneumonia. The second type of spread was characterized by development of successive secondary fans a few days apart, resembling a "creeping" pneumonia.

Resolution was usually rapid with complete clearing in a few weeks but one case required three months. The soft hazy appearance of the early infiltrate gradually changed to that of a more organized type usually in a few days after the maximum extent of the lesion was reached. Steady progressive clearing of the pseudo-fibrotic infiltration was the rule and periods of more than one week without definite change in X-ray shadows were rare.

Frequently there was marked resemblance to active tuberculosis especially in upper lobe infiltrations during the stage of resolution. Cases initially dis-

covered during this period required further clinical study and serial films for differentiation

Luncheon Session

Following the luncheon, Dr. David R. Lyman, of Gaylord Farm Sanatorium, Wallingford, Connecticut, gave a most delightful talk during which he reminisced over his early days in tuberculosis work at Trudeau and Gaylord Farm.

Afternoon Session

Coexisting Syphilis and Tuberculosis in the Negro by Reuben Hoffman, M.D., Maryland Tuberculosis Sanatorium, Henryton, Maryland.

This paper will be published in full in one of the forthcoming issues of the REVIEW.

Tuberculous Bronchitis: Its Effect on the Behavior, Pattern and Treatment of the Pulmonary Disease by H. McLeod Riggins, M.D., Medical Director, and Robert P. Gearhart, M.D., Asst. Visiting Physician, Triboro Hospital, New York City.

In the majority of papers dealing with tuberculous bronchitis, the bronchial condition *per se* has been emphasized. This paper was directed primarily to the effect the bronchial disease has on the pattern, behavior and treatment of the pulmonary disease, or diseases.

The reader discussed the effect of tuberculous bronchitis upon the function of the bronchi from the viewpoint of bacteriology and changed morphology. This was followed by a detailed analysis of the secondary pulmonary conditions resulting from the tuberculous bronchitis, in the following order:

1: The development of active pulmonary tuberculosis.
2: Bronchogenic spread of the tuberculosis.
3: Exacerbation of quiescent tuberculosis.
4: The development of suppurative pneumonia and putrid abscess.
5: The development of bronchiectasis.
6: The development of tension or positive pressure cavity and obstructive emphysema.
7: The development of atelectasis.

Because of the great variety of pathological changes resulting from the tuberculous bronchitis, stress was placed upon the need for careful individualization in the management of the diverse types and in the application of various therapeutic measures.

Courageous action instituted early, prior to the development of "malignant" complications, should improve the prognosis of many individuals who previously experienced dire consequences with conservative treatment.

Indications and Risks Involved in Pulmonary Resection for Pulmonary Tuberculosis by Richard H. Overholt, M.D., Brookline, Massachusetts.

Extirpative therapy has proved effective in the management of an increasing

number of otherwise hopeless pulmonary cases of cancer, lung abscess and bronchiectasis. There is justification now for renewed hope that certain heretofore fatal types of tuberculosis may also be saved by removal of the involved lung. This optimism is based upon a ten-year experience with 77 operations upon 75 patients. Improved methods of hilar dissection, meticulous bronchial closure and the local use of sulfa drugs have minimized complications and lowered the operative mortality. In 1942 and 1943, in 46 consecutive reasonable risk cases, the operative mortality was 5.2 per cent. There were no wound infections and permanent bronchial fistula developed in not a single case. Thirteen per cent showed spread or exacerbation of the disease in the remaining lung, but in half of these there was subsequent clearing.

In the beginning most patients were treated because a double disease was present, tuberculosis plus bronchiectasis. Next, thoracoplasty failures were accepted. More recently the indication for extirpation in the majority of patients has been the presence of a lesion with fatal potentialities in which failure of other forms of treatment was predicted. The fatal types of tuberculosis have included those (*1*) complicated by bronchial disease, (*2*) showing rapid progression, (*3*) giant cavitation, (*4*) basilar disease, (*5*) extensive multilobular predominantly unilateral tuberculosis.

It has been demonstrated that pulmonary resection in the presence of tuberculosis is possible and can be done with little risk and few complications. It has also been demonstrated that a tuberculous lung offers no unusual technical problems of resection. The tuberculous subject presents no unusual problem in wound healing or in bronchial closure. If lesions with fatal potentialities exist and if the contralateral lung is healthy or has disease which is controlled or controllable, serious consideration to pulmonary resection should be given. Lobectomy, unilateral or bilateral, and pneumonectomy may prove to be the most conservative form of treatment for certain patients.

Evening Session

Informal conference devoted to the discussion of interesting and unusual cases followed by:

Symposium and Panel Discussion on Dust Inhalation Diseases of the Lungs conducted by the Clinical Section on Chronic Pulmonary Diseases, Tuberculosis Sanatorium Conference of Metropolitan New York.

I. *Practical Clinical Aspects*

J. Burns Amberson, M.D
Visiting Physician-in-Charge
Chest Service
Bellevue Hospital

II. *Panel Discussion*

Foster Murray, M.D., *Moderator*
Director of Tuberculosis Service
Kingston Avenue Hospital

Andre F. Cournand, M.D.
Assistant Professor of Medicine
Columbia University College of Physicians and Surgeons

Leopold Brahdy, M.D.
Physician-in-Charge of Occupational Diseases of Employees of the City of New York

Leonard Greenburg, M.D.
Executive Director
Division of Industrial Hygiene
New York State Department of Health

All of the papers were followed by lively discussions. Attendance was surprisingly large in spite of present difficulties.